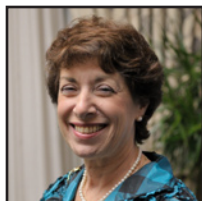


February 2011

NIEHS Spotlight



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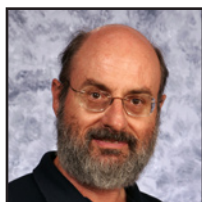
[Measuring efforts to translate science into public health action](#)

At a special workshop Jan. 10, NIEHS formally launched its new Evaluation Metrics Manual to help measure the progress of outreach and translation goals.



[NIEHS-supported database joins TOXNET](#)

A massive new public database supported in part by NIEHS is now a part of TOXNET, the U.S. National Library of Medicine's portal for toxicology data.



[James Mason elected AAAS fellow](#)

This month, Principal Investigator James Mason, Ph.D., joins a small group of his colleagues at NIEHS who have been honored as fellows of the AAAS.

Science Notebook



[NTP workshop investigates links between chemicals and obesity](#)

New research is emerging that suggests environmental exposures may also play a significant role in the risks associated with developing diabetes and obesity.



[Miller explores the longest signaling pathway in endothelial cells](#)

The brain's most effective defense against neurotoxins is also the greatest hindrance in the delivery of potentially life-saving medicines to the central nervous system.



[Mismatch base pairing is structurally similar to correct base pairing](#)

NIEHS study findings represent the first evidence of the "spontaneous base substitutions due to tautomeric forms" proposed by Watson and Crick in 1953.



[Faculty of 1000 highlights study by Korach group](#)

F1000 Editor-in-Chief Sarah Greene told Korach that his paper's selection "places your work in our library of the top two percent of published articles in biology and medicine."



[NIEHS clinical researchers highlighted in JAMA](#)

NIEHS clinical researchers are promoting a new systematic methodology for treatment of and research into a mysterious and debilitating autoimmune disease.

NIEHS Spotlight



[Center grantees named AAAS fellows](#)

Neurobiologist Marie-Francoise Chesselet, M.D., Ph.D., and exposure science expert Barbara J. Turpin, Ph.D., are being honored for their NIEHS-supported research.



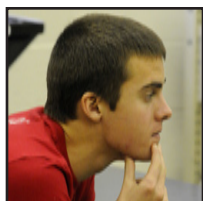
[Superfund researcher honored by AAAS](#)

The premier scientific society recognized Agnes Kane, M.D., Ph.D., for contributions to understanding of the health impact of asbestos and another inhaled particulates.



[Androphy selected for 2011 "Top 5" leadership class](#)

Director of the NIEHS Ethics Office Bruce Androphy, J.D., will be among the select group of leaders participating in the 2011 NIH Executive Leadership Program.



[Students confront the human health effects of climate change](#)

EHP Science Education Program staff were guest instructors in advanced placement environmental science classes at Orange High School in Hillsborough, N.C.



[NIEHS takes its message on the road](#)

NIEHS scientists will showcase their research and funding programs at conferences all over the nation again this year.

Science Notebook



[Are plastics without estrogenic-active compounds possible?](#)

Results of an experimental cell assay could lead to the development of commercially available products that do not exhibit detectable estrogenic activity.



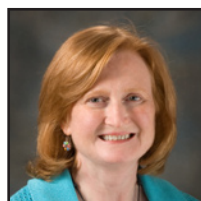
["Phosphorylopathies," a new class of human disorders](#)

According to David Armstrong, Ph.D., a single nucleotide change in an ion channel gene could result in pronounced functional changes by altering phosphorylation.



[Environmental toxicants transfer from mother to baby](#)

An international team of scientists led by Philippe Grandjean, M.D., Ph.D., measured concentrations of 87 environmental chemicals in both maternal and fetal tissues.



[Assigning a function to histone modifying enzymes](#)

Sharon Dent, Ph.D., a leading scientist in the field of chromatin biology, may have had a sense of déjà vu on her recent visit to give a presentation at NIEHS Jan. 13.



[NTP Alternatives Center Holds Workshops on Best Safety Testing](#)

Several alternative testing methods offer federal public health agencies and regulated industry important new tools for assessing the safety of chemicals and products.

NIEHS Spotlight



[NAS series continues with workshop on microbiome](#)

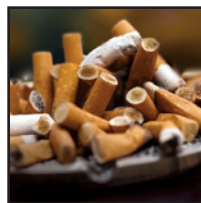
Sponsored by NIEHS, the program holds three workshops per year on the use of new discoveries, tools, and approaches for guiding environmental health decisions.



[Search opens for NIEHS associate director for management](#)

NIEHS is now accepting applications for the position of associate director for management. Applications will be accepted through Feb. 14.

Science Notebook



[This month in EHP](#)

With its image of an ashtray overflowing with cigarette butts, the cover of the latest issue of EHP is a fitting backdrop for the journal's feature story on thirdhand smoke.



[Upcoming distinguished lecture by Maiken Nedergaard](#)

Nedergaard will explore emerging issues in translational neuromedicine in a presentation titled "Astrocyte — The Other Cell in Brain."

Inside the Institute



[NIEHS remembers Martin Luther King Jr.](#)

NIEHS welcomed state Rep. Henry M. (Mickey) Michaux Jr. as guest speaker for a Jan. 19 tribute to the legacy of civil rights leader Martin Luther King Jr.

Extramural Research

[Extramural papers of the month](#)

- [Mitochondrial dysfunction in children with autism](#)
- [DNA damage mapped out](#)
- [Less toxic and more effective carbon nanotubes for drug delivery](#)
- [Sperm may be harmed by BPA exposure](#)

Intramural Research

[Intramural papers of the month](#)

- [MicroRNA in glucocorticoid-induced lymphocyte apoptosis](#)
- [Ubiquitination through lysine 63 mediates adhesion and migration of MDA-MB-435 cells](#)
- [The function of BAF155 in the SWI/SNF chromatin remodeling complex](#)
- [Mutation of proline 180 markedly reduces the rate of desensitization of nAChR](#)

Calendar of Upcoming Events

- **Feb. 1** in Rodbell Auditorium, 8:00 a.m.-5:00 p.m. — NIEHS Centers for Disease Investigation through Specialized Clinically-Oriented Ventures in Environmental Research (DISCOVER): Presentations on Research Approach and Early Findings
- **Feb. 1 (Offsite Event)** in Room 147, Nanaline Duke Building on the campus of Duke University, 12:30-1:30 p.m. — Tuesday Seminar Series with Mike Resnick, Ph.D., topic TBA
- **Feb. 2-3 (Offsite Event)** at the U.S. Environmental Protection Agency Auditorium C111 A/B, in Research Triangle Park, N.C. — Air Pollution and Brain Health Workshop
- **Feb. 3** in Keystone 1003AB, 2:00-3:00 p.m. — Debora Cory-Slechta, Ph.D., speaks on “Consequences of Combined Exposures to Lead and Stress for Cognitive Functions,” as part of the Keystone Science Lecture Seminar Series
- **Feb. 7** in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Laboratory of Molecular Genetics Fellows Invited Guest Lecture, featuring Thomas Kensler, Ph.D., topic TBA
- **Feb. 7** in Rodbell Auditorium, 2:00-3:00 p.m. — Clinical Director’s Seminar Series with Richard Cannon, M.D., discussing “Diabetes Risk in the Workforce: NHLBI’s Keep the Beat Program”
- **Feb. 8** in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture Series presentation by Maiken Nedergaard, M.D., talking on “Astrocyte – The Other Cell in Brain”
- **Feb. 11 (Offsite Event)** at the Searle Center on the campus Duke University, 8:30 a.m.-5:00 p.m. — “Beyond the Brink: Addressing Human Health and Security in a Changing Climate,” a symposium hosted by the Duke Global Health Institute and the Student International Discussion Group [register](#)
- **Feb. 16-17** in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — National Advisory Environmental Health Sciences Council meeting
- **Feb. 25** in Rodbell Auditorium, 10:00-11:30 a.m. — Keystone Lecture Seminar Series with Atul Butte, M.D., Ph.D.
- **Feb. 28** in Rodbell Auditorium, 8:00 a.m.-5:00 p.m. — North Carolina Association for Biomedical Research “Prescription for Science Literacy”
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

SOT to celebrate 50th anniversary benchmark

By Ed Kang

NIEHS and NTP scientists, including Director Linda Birnbaum, Ph.D., will be among the 7,000 toxicologists from 50 countries expected to attend the Society of Toxicology's (SOT) 50th annual meeting from March 6-10 in the nation's capital. While the conference traditionally provides a thought-provoking program that captures the latest scientific advances of the prior 12 months, this year's event will also showcase a host of celebratory events, publications, and sessions befitting a golden anniversary celebration.



One such commemoration is a special poster titled “Benchmarks in Toxicology” that will be unveiled at the meeting. Created by NIEHS/NTP, the journal *Environmental Health Perspectives*, and SOT, the poster will showcase the people, innovations, discoveries, and events that have been milestones in the development of the field.

“This poster will be something special, and it draws upon themes that resonate with the toxicology community,” said Birnbaum, who was president of the Society in 2004. “I’m thrilled that more than 200 nominations for benchmarks were received from SOT members — everything from historical figures to the latest mechanistic research.” The nominations were carefully reviewed for relevance by a distinguished scientific panel, including several former SOT presidents.

Visitors to the conference will be able to take home their own commemorative poster, which will be available at the NIEHS booth and throughout the conference venue.

In addition to the poster, NIEHS and NTP scientists will also be featured in dozens of scientific sessions and workshops. Among them, staff from the NIEHS Division of Extramural Research and Training (DERT) will be on-hand to discuss grant opportunities, and Birnbaum will speak March 9 at 9:30 a.m. about the future directions of NIEHS and the NTP and emerging trends in toxicology research.

Other keynote speakers for the 50th annual meeting include Francis Collins, M.D., Ph.D., director of the National Institutes of Health; Margaret Hamburg, M.D., commissioner of the U.S. Food and Drug Administration; Lisa Jackson, administrator of the U.S. Environmental Protection Agency; and John Howard, M.D., director of the National Institute for Occupational Safety and Health.



Birnbaum, left, is shown with one of the many people she talked with at the 2010 SOT meeting about one of her favorite topics — the importance of NIEHS efforts in the quest to improve public health. (Photo courtesy of Ed Kang)

Throughout the weeklong event, NIEHS and NTP scientific and program staff will be providing live updates on all the innovations, breakthrough research, award presentations, and interesting people that make SOT so unique. The updates will be posted on the NIEHS SOT [Web site](#) and on [Twitter @LiveatSOT](#).

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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EHP Science Education Program expanding

By Matt Goad

The NIEHS journal [Environmental Health Perspectives \(EHP\)](#) is expanding the reach of its Science Education Program with the launch of a new and improved Web site and redesigned lessons. The move represents a heightened commitment to science education outreach by the journal.

The EHP Science Education Program promotes knowledge of environmental health to high school and undergraduate students to make them better stewards of their health and their environment, according to Bono Sen, Ph.D., science education and outreach program manager at EHP.



[Listen as Sen discusses the expanded Science Education Program with EHP Podcast Host Ashley Ahearn](#)

[Read Transcript](#)

It is the only program of its kind offered by a scientific journal, Sen said, featuring lessons that build upon selected news and research articles published in the journal. “The science is up-to-date and relevant, and the lessons encourage students to learn actively about their health and their environment through hands-on and critical thinking activities,” she said.

The lessons, which are aligned with the [National Science Education Standards](#), are arranged into six modules:



Air — discussing topics related to air quality monitoring, air pollution, and the impact of air pollution on human health



Water — investigating issues of water resources, pollution routes of exposure, sources of pollution, health effects, and policy



Land — including topics related to land-use hazards, built environments, and the perils of impervious surfaces



Climate — exploring energy issues, environmental and human impacts of climate change, alternative fuels, disaster, and emergency preparedness



Food — addressing topics related to genetically modified and organic foods, the presence of pesticides and additives in foods, and obesity



Disease — examining topics related to the genetic basis of disease, disease risk factors, and environmental toxicants

In addition to offering free resources in English and Spanish, EHP also offers free professional development workshops to teachers to enhance their understanding of environmental health related topics to bring back to their classrooms and communities.

The program not only brings teachers to NIEHS, it sends Sen and her partner in the outreach effort, EHP Science Education and Outreach Program Coordinator Carly Carroll, out into nearby schools to engage with students ([see related story](#)).

In collaboration with the Environmental Protection Agency, the EHP Science Education Program will host its first high school student workshop this coming summer. With a focus on climate change, this workshop will educate students about environmental health and sciences and related careers in science, technology, engineering, and math (STEM).

The program also provides various outreach training opportunities for the institute's postdoctoral fellows by providing teaching opportunities during the teacher workshops and writing opportunities with the EHP lessons.

Sen has plans to set up a teacher advisory board to guide the creation and evaluation of new materials for the program, and she is building a partnership network with science education professionals nationwide.

For more information visit the Science Education Program [Web site](#).

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Sen, right, and Carroll are utilizing local and long-distance partnerships and resources to enhance the utility of research published in EHP for science teachers worldwide. (Photo courtesy of Steve McCaw)

Measuring efforts to translate science into public health action

By Eddy Ball



NIEHS took a step toward helping grantees measure the progress of outreach and translation goals at a workshop Jan. 10, with the formal launch of its new [Evaluation Metrics Manual](#). The manual targets programs in the NIEHS [Partnerships for Environmental Public Health \(PEPH\)](#) program ([see text box](#)) with guidance for researchers and program staff on ways to use logic models to define what constitutes success and how to measure it.

Led by the manual's senior author, NIEHS Program Analysis Branch Chief Christie Drew, Ph.D., the workshop was the first in a series of training and information-gathering sessions expected to continue through February.



Linked video:
[Watch as Director of DERT, Gwen Collman, Ph.D., discusses the goals of the PEPH program \(02:41\).](#)

(Launches in new window)

Download Media Player:  Quicktime 

“Part of the challenge is that many products that are developed by PEPH outreach and translation activities do not make it into the typical peer-reviewed literature, which is how NIH often measures the progress of knowledge creation,” Drew said. “So we need to think about what other kinds of approaches we can use to document grantee success.”

A work in progress

Drew emphasized that the draft is not a prescriptive design for planning and evaluation, but a collection of tangible examples from effective programs representing a starting point for what should be seen as a dynamic, living document. She encouraged public comments on the draft through an evaluation metrics [feedback form](#) or by [e-mail](#), and offered to schedule webinars for interested groups. She described the process as an ongoing partnership effort by NIEHS staff and grantees from a range of programs funded by the NIEHS Division of Extramural Research and Training (DERT).

The effort to develop evaluation metrics, Drew explained, addresses public responses to a 2007 “[Request for Information: Partnerships for Environmental Public Health](#)” and participant comments during a subsequent PEPH [workshop](#) held in June 2008.

PEPH programs and similar efforts funded by a variety of other organizations typically form partnerships with communities and stakeholders, to conduct and translate environmental health science research into new policies and programs to improve public health. While the goals may be clear — a policy decision by a government body or the removal of a potential health threat from a community, for example — in many cases, the specific steps toward those goals can be harder to define and even more challenging to measure.

A logic model for evaluation

The manual employs a logic model framework to analyze how programs can potentially use various resources or inputs to conduct a range of activities that generate a series of products or outputs to realize benefits or impacts. It focuses on five key program activity areas — partnerships, leveraging, products and dissemination, education and training, and capacity building for communities, researchers, healthcare professionals, and decision makers.



NIEHS DERT Director Gwen Collman, Ph.D., welcomed workshop participants. “It became apparent years ago that there weren’t very many metrics related to evaluation that were readily available,” she told the audience. (Photo courtesy of Steve McCaw)



Drew explained that NIEHS is not trying to prescribe program evaluation procedures. “What we are trying to do with this manual is to show you how you can come to those metrics yourself,” she said. (Photo courtesy of Steve McCaw)



The workshop attracted science education outreach specialists, including, from foreground, Bono Sen, Ph.D., Environmental Health Perspectives (EHP) science education outreach program manager; Carly Carroll, EHP science education program coordinator; Kelly Leovic, Environmental Protection Agency environmental education program manager; and Ericka Reid, Ph.D., NIEHS education outreach specialist. (Photo courtesy of Steve McCaw)

The manual's appendices include a list of NIEHS staff and subject expert discussants and discussant dates, additional evaluation resources, a combined bibliography of the more than 150 references cited in the manual, and a cross index of examples and chapter sections.

To review the manual and provide comments, visit the PEPH [Web site](#).



Social Research Specialist Alison Gunn, representing the Clinical and Translational Science Awards program at the University of North Carolina at Chapel Hill, was at the workshop to learn more about the new manual. Seated to her right is colleague Zoe Enga, evaluation and data coordinator. (Photo courtesy of Steve McCaw)



Program Analyst Liam O'Fallon oversees NIEHS environmental justice grants. He told the audience that a better understanding of metrics would help NIEHS staff as well benefit grantees. (Photo courtesy of Steve McCaw)

Partnerships for Environmental Public Health (PEPH) – an umbrella program at NIEHS

With its roots in environmental justice and community-based participatory research programs, PEPH brings together scientists, community members, educators, health care providers, public health officials, and policy makers in the shared goal of advancing the impact of environmental public health research at local, regional, and national levels. The program emphasizes both scientific advances and the development of practical materials for use in communities, with a focus on translating research findings into tools, materials, and resources that can be used by a variety of audiences to prevent, reduce, or eliminate adverse health outcomes caused by environmental exposures.

Members of PEPH conduct programs funded by a broad range of funding mechanisms, including center grants for the promotion of children's and women's environmental health, outreach and translation components of the Superfund Research Program, and education and training funded by the Worker Education and Training Program. The program's cross-divisional emphasis facilitates communication among partners who might otherwise have few opportunities to share their successes and challenges with one another.



Members of the evaluation metrics team were on hand to help field questions about the manual. Shown above are Program Analyst Helena Davis, right, and Health Scientist Administrator Kristi Pettibone. (Photo courtesy of Steve McCaw)

NIEHS-supported database joins TOXNET

By Eddy Ball

A new report from a team of scientists led by NIEHS grantee Carolyn Mattingly, Ph.D., presents an update on a massive public database supported in part by NIEHS that is now a part of [TOXNET \(TOXicology Data NETwork\)](#), the U.S. National Library of Medicine's portal for toxicology data.

According to [Mattingly](#), the new resource, known as the [Comparative Toxicogenomics Database \(CTD\)](#), is a powerful tool that will contribute substantively to the emerging field of predictive toxicology by providing curated data from the literature to enhance understanding about the connections between chemicals, genes and proteins, and diseases.

Funded in part by an NIEHS [grant](#) awarded in 2005, CTD was developed by scientists at the [Mount Desert Island Biological Laboratory \(MDIBL\)](#) in Maine, where Mattingly is an associate professor. The project receives additional funding from NIH's National Center for Research Resources (NCRR) and through a collaborative research project with the pharmaceutical giant Pfizer to investigate 1,500 chemical compounds that may be useful in drug development.

As Mattingly said in a Nov. 11, 2010 [interview](#) with the Bar Harbor (Maine) Times, CTD is an effort to compile and organize increasingly copious amounts of formal research on the relationship between chemicals, genes, and disease ([see text box](#)). The database is an attempt to map the complex ways in which chemicals are related to diseases. CTD is part of a larger effort to track the approximately 85,000 chemicals used in American industry — the overwhelming majority of which have never been subject to rigorous testing or regulation.

In the [study](#), which appeared in the January issue of Nucleic Acids Research, Mattingly explained why the CTD is unique among the other resources in the TOXNET suite of integrated databases. "CTD provides detailed information about chemical–gene interactions, chemical-disease relationships, and gene-disease relationships," the CTD team wrote. "By integrating these core data with other datasets, CTD helps turn knowledge into discoveries by identifying novel connections between chemicals, genes, diseases, pathways, and GO [gene ontology] annotations that might not otherwise be apparent using other biological resources."

TOXNET is a cluster of databases covering information on toxicology, hazardous chemicals, environmental health, and other related areas. The network is managed by the [Toxicology and Environmental Health Information Program](#) in the [Division of Specialized Information Services](#) of the [U.S. National Library of Medicine](#). CTD is the twelfth database in this growing publicly accessible family of databases.

Mattingly's grant is overseen by NIEHS Program Administrator David Balshaw, Ph.D.



Mattingly said of her work with CTD, "This effort is significant, because there are a tremendous number of chemicals in commerce..., [and] we really don't understand their mechanisms of action or their consequences on our health."
(Photo courtesy of Carolyn Mattingly)

Harnessing massive amounts of information with an integrated database

In her Bar Harbor Times interview, Mattingly offered an example of how querying the nearly 300,000 direct and indirect chemical-disease interactions charted in the database could help researchers better understand potential links between a chemical and diseases. Entering “bisphenol A” in the database, for example, will yield connections with many potentially associated diseases, including schizophrenia, leukemia, and melanoma. Researchers can then explore the data more closely as they formulate hypotheses about chemical-disease connections and underlying mechanisms.

Several analysis tools are integrated with the database to facilitate access to and interpretation of data in CTD. For example inferred chemical-disease associations can be ranked statistically and Venn diagrams can be generated, to either compare researchers’ data to CTD data or to disease associations or mechanisms of action among chemicals.

According to Mattingly, the integrated data about chemical-gene/protein interactions and chemical- and gene-disease relationships enable scientists to develop novel hypotheses about the origins of environmentally influenced diseases.

Citation: [Davis AP, King BL, Mockus S, Murphy CG, Saraceni-Richards C, Rosenstein M, Wiegers T, Mattingly CJ](#). 2011. The Comparative Toxicogenomics Database: update 2011. *Nucleic Acids Res* 39(Database issue):D1067-D1072.

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James Mason elected AAAS fellow

By Eddy Ball

This month, Principal Investigator James Mason, Ph.D., joins a small group of his colleagues at NIEHS who have been honored as fellows of the AAAS (American Association for the Advancement of Science). The organization will present Mason with a certificate and rosette Feb. 19 in Washington, D.C., during the AAAS Fellows Forum, which is part of the [AAAS Annual Meeting](#).

[Mason](#) is head of the Drosophila Chromosome Structure Group in the NIEHS Laboratory of Molecular Genetics. He serves on the editorial boards of the *International Journal of Biological Sciences* and *Journal of Biomedicine and Biotechnology*.

Mason’s research explores genome stability and DNA repair, an organism’s response to the internal stress of replication and to environmental insults, such as ionizing radiation. His group studies chromatin structure and alterations that impact gene expression, especially in regard to the function of structures found at the ends of chromosomes known as telomeres, which play a key role in aging, cancer, and many diseases.



*Newly elected AAAS Fellow James Mason
(Photo courtesy of Steve McCaw)*

In his congratulatory letter to Mason, AAAS Chief Executive Officer Alan Leshner, Ph.D., wrote, “You are being honored for distinguished contributions to the field of chromosome structure, particularly showing that there are alternatives to telomerase in maintaining telomeres, especially the use of transposons.” Leshner said that Mason is joining members elected by the AAAS Council each year in recognition of “efforts on behalf of the advancement of science or its applications [which] are scientifically or socially distinguished.”

Founded in 1848, AAAS serves some 262 affiliated societies and academies of science, serving 10 million individuals. The AAAS journal *Science* has the largest paid circulation of any peer-reviewed general science journal in the world, with an estimated total readership of one million.

AAAS began electing fellows in 1874, an honor bestowed upon members by their peers. Fellow nominations may be made by the Steering Groups of the Association’s 24 sections, by the chief executive officer, or by any three fellows who are current AAAS members, so long as two of the three sponsors are not affiliated with the nominee’s institution. Each nominee must receive the approval of a majority of the Steering Group members.

Mason joined NIEHS in 1978 after completing a postdoctoral fellowship at the University of California, Davis. He has published more than 67 peer-reviewed articles in leading biomedical journals, as well as several book chapters. As part of his scientific community service at NIEHS, Mason chairs the NIEHS Committee on Promotion III, which last year developed revised guidelines and procedures for deciding on promotions to GS-12 for scientists working as biologists and chemists in the Institute’s Division of Intramural Research ([see story](#)).

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Center grantees named AAAS fellows

By Eddy Ball

Two NIEHS centers grantees, neurobiologist Marie-Francoise Chesselet, M.D., Ph.D., and exposure science expert Barbara J. Turpin, Ph.D., are among scientists elected as 2010 American Association for the Advancement of Science (AAAS) Fellows.

[Chesselet](#) is the director of the NIEHS-funded Center for Gene Environment Studies in Parkinson’s Disease at the University of California, Los Angeles (UCLA) [Center for the Study of Parkinson’s Disease](#) (PD).

In good company

Mason joins a group of NIEHS scientists elected as AAAS Fellows in previous years:

- Joel Abramowitz, Ph.D., special assistant to the scientific director
- Marian Johnson-Thompson, Ph.D., former director of Education and Biomedical Research Development
- James Putney, Ph.D. principal investigator and head of the Calcium Regulation Group in the Laboratory of Signal Transduction
- Anne Sassaman, Ph.D., director emeritus of the Division of Extramural Research and Training
- Barbara Shane, Ph.D., former NTP staff scientist and executive secretary of the NTP Board of Scientific counselors
- Samuel Wilson, M.D., principal investigator and head of the DNA Repair & Nucleic Acid Enzymology Group in the Laboratory of Structural Biology
- Jerrel Yakel, Ph.D., principal investigator and head of the Ion Channel Physiology Group in the Laboratory of Neurobiology

Currently the Charles H. Markham Professor of Neurology and chair of the Department of Neurobiology in the David Geffen School of Medicine at UCLA and author of more than 135 peer-reviewed manuscripts and 50 book chapters and reviews, she held faculty appointments at the Medical College of Pennsylvania and University of Pennsylvania before joining UCLA in 1996.

[Turpin](#) is a member of the NIEHS-funded [Center for Environmental Exposures and Disease \(CEED\)](#), which is jointly sponsored by Rutgers and the University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School. She joined the Rutgers faculty in 1994 and has more than 80 peer-reviewed publications. She is a professor in the Department of Environmental Sciences at the Rutgers University School of Environmental and Biological Sciences.

Chesselet and Turpin will each receive an official certificate and a gold and blue rosette pin Feb. 19 during the AAAS Fellows Forum during the 2011 AAAS Annual Meeting in Washington, D.C.

Environmental pesticides and risk for PD

Chesselet and colleagues at the UCLA center have discovered associations between high levels of exposure to specific environmental pesticides and PD and are building on this knowledge to determine the mechanisms of action that may be causing this association. They use an integrated, multidisciplinary approach to identify molecular pathways that are disrupted by these pesticides, identify additional agricultural pesticides that share similar mechanisms, and determine whether these also increase the risk of PD.

Supported by a Centers for Neurodegeneration Science [grant](#) managed by Program Administrator Cindy Lawler, Ph.D., the group is gaining a better understanding of the potential neurotoxicity of widely used pesticides, in an effort to protect the health of workers and the general population.

Air pollution, health, and climate change

In its announcement of her election, AAAS cited Turpin “for major contributions to our basic knowledge of the properties and effects of organic aerosols.” Turpin investigates atmospheric chemical transformations that convert gaseous pollutants into aerosols — tiny solid particles and liquid droplets suspended in the air that are associated with increased heart attacks, reduced visibility, and climate change.

CEED, which is directed by Principal Investigator Helmut Zarbl, Ph.D., is supported by an NIEHS Environmental Health Sciences Center [grant](#) first awarded in 1988 and managed by NIEHS Program Administrator Les Reinlib, Ph.D. Turpin is a co-author on 13 of the nearly 800 publications associated with CEED’s NIEHS funding.



Chesselet smiled as she responded to a question during a meeting of the Parkinson's Centers at NIEHS in October 2006. (Photo courtesy of Steve McCaw)



Turpin's previous honors include the Cook College/New Jersey Agricultural Experiment Station (NJAES) Research Excellence award presented by Rutgers University. (Photo courtesy of Barbara Turpin)

A premier scientific society

Founded in 1848, AAAS serves some 262 affiliated societies and academies of science, serving 10 million individuals. The AAAS journal *Science* has the largest paid circulation of any peer-reviewed general science journal in the world, with an estimated total readership of one million.

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Superfund researcher honored by AAAS

By Eddy Ball

The American Association for the Advancement of Science (AAAS) will honor NIEHS Superfund Research Program grantee Agnes Kane, M.D., Ph.D., as one of its newly elected Fellows at its annual meeting Feb. 19. Along with those of four colleagues at Brown University, her election was announced by the university Jan. 11.

According to the Brown University [press release](#), AAAS recognized Kane for "research contributions to the mechanistic understanding of the impact of asbestos and other inhaled particulates on the evolution of disease and for her leadership role in education and advising on national and international policies concerning environmental toxicology."

A focus on asbestos

Kane is a professor and chair of the Department of Pathology and Laboratory Medicine at Brown University where she has pursued research on fiber toxicology and nanotoxicology funded continuously by NIEHS since 1992 with additional support from the U.S. Environmental Protection Agency and National Science Foundation. Kane is board certified in anatomic pathology and has studied murine models of asbestos-induced disease.

Recognized as a leader in her field, Kane was a plenary speaker at a December 2009 workshop convened by NIEHS in Chapel Hill, N.C. on the topic, "Asbestos and Related Mineral Fibers: State of the Science and Mode of Action" ([see story](#)). The review articles from that workshop have been accepted by the *Journal of Toxicology and Environmental Health, Part B: Critical Reviews*, and are expected to be published in late summer or early fall 2011. Kane is lead author on the article, "Non-Neoplastic and Neoplastic Pleural Endpoints Following Fiber Exposure."

Kane directs the Training Program in Environmental Pathology at Brown and the Training Core for the Superfund Research Program Grant, funded by a [grant](#) managed by Health Scientist Administrator Heather Henry, Ph.D. She is also the principal investigator on NIEHS grants for [training](#) and individual-research on [nanocarbon toxicity](#) from NIEHS.



*In her discussion at the NIEHS meeting on asbestos, Kane said, "There's a lot more we don't know about these [asbestos and related mineral fiber] diseases than we do know."
(Photo courtesy of Steve McCaw)*

AAAS Fellows

AAAS began electing fellows in 1874, an honor bestowed upon members by their peers. Fellow nominations may be made by the steering groups of the Association's 24 sections, by the chief executive officer, or by any three fellows who are current AAAS members, so long as two of the three sponsors are not affiliated with the nominee's institution. Each nominee must receive the approval of a majority of the steering group members.

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Androphy selected for 2011 "Top 5" leadership class

By Eddy Ball

Director of the [NIEHS Office of Ethics](#) Bruce Androphy, J.D., will be among a select group of leaders participating in the 2011 [NIH Executive Leadership Program \(ExLP\)](#). Beginning its second year of training, the ExLP is a competitive leadership program geared towards aspiring and existing "Top 5" leaders at NIH — those currently in top leadership roles or likely to assume one within the next five years.

Androphy will participate in orientation Feb. 15 on the NIH campus in Bethesda, Md., and a series of retreats, training sessions, and special events throughout the spring, summer, and fall of this year, concluding with a session at the Brookings Institution Sept. 21-22.

Androphy is the second NIEHS leader to participate in the program. NIEHS Director of the Division of Extramural Research and Training Gwen Collman, Ph.D., was a member of the ExLP's first group, which graduated 22 leaders from NIH Institutes and Centers (ICs) Sept. 22, 2010. Collman became one of the Top 5 with her appointment as permanent director of DERT in December 2010 ([see story](#)).

About ExLP

The ExLP is a rewarding leadership experience that integrates the hands-on involvement of senior NIH executives and the academic experience of NIH's educational partners, Brookings Executive Education and Washington University in St. Louis. Key features of the upcoming program include the following experiences:

- Content theme training — "Leading at the Top," "Executive Communications," "Policy Making on the Hill" and "Leading in Networks"
- Opportunities to participate and/or lead high-priority workgroups and committees
- Peer advising and mentoring
- Leadership coaching and 360 degree assessments — comprehensive self- and peer-reviews of leadership quality
- Access to NIH executives in the form of panel discussions, themed lectures, and special events



*Androphy, who joined NIEHS in December 2009, has been instrumental in reorganizing the NIEHS ethics program and expanding the scope of its services for NIEHS employees.
(Photo courtesy of Steve McCaw)*

Director of the NIEHS Office of Ethics Bruce Androphy

Prior to joining NIEHS, Androphy served for nearly three years as the first executive director of the Tennessee Ethics Commission, established in 2006. In that role, he oversaw the Commission staff, was responsible for the commission's operations and mission, and advised the commission members. He dealt extensively with members of the Tennessee state legislature and legislative lobbyists.

Before assuming his position in Tennessee, Androphy was general counsel to the New York State Ethics Commission, where he worked for almost 17 years. As general counsel, he was involved in issues surrounding state-sponsored scientific research. He is a member of the Council on Governmental Ethics Laws (COGEL), an international government ethics society that includes NIEHS as a member organization.

A graduate of the University of Pennsylvania, Androphy received his law degree from George Washington University National Law Center in Washington, D.C.



Collman, front row center in purple, joined colleagues for an ExLP commencement photo. The ceremony featured Top 5 leaders with Lawrence Tabak, D.D.S., Ph.D., NIH principal deputy director, and Colleen Barros, NIH deputy director for management. (Photo courtesy of NIH Training Center)

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Students confront the human health effects of climate change

By Matt Goad

The [Science Education Program](#) staff at the journal Environmental Health Perspectives (EHP) say they always enjoy visiting classrooms and talking to students about the scientific process and how scientists collect data to address key scientific questions. Program Manager Bono Sen, Ph.D., and Program Coordinator Carly Carroll had an opportunity to just do that, when they visited Orange High School in Hillsborough, N.C. Jan. 5.

During their visit, they gave a presentation on the complexities of climate change to students in teacher Nina Daye's advanced placement environmental science class, taking the students through a reading, small-group discussion, and hands-on exercise about the human health impacts of climate change based on one of the [lesson plans](#) they've developed using research published in EHP.

“Much of the instruction about climate change in schools is taught from the ecological perspective. Learning about the effects of climate change on human health will be key to engaging the students’ interest in climate change science,” Sen said. Daye agreed that looking at climate change from a human health perspective brings home the message.

“I think when people start to think, ‘How’s it going to affect my health?’ it has more of an impact,” Daye said. “It’s not, ‘Oh, it’s just polar bears.’”

Sen and Carroll had the students complete an exercise to demonstrate how complex the climate change scenario is and how it will aggravate some existing diseases, while creating opportunities for others, such as malaria, to flourish in environments where they are currently not found. A key aspect of climate change education that Sen and Carroll want to impress upon the students is that climate change will impact not only the developing world but also the U.S.

Making the connections between climate and health

After introducing the lesson, Sen and Carroll divided the students into groups of five and assigned each group a disease to study, such as asthma or cancer. The students read a condensed version of the original information presented in an EHP research white paper. They identified the environmental impact — such as increase in temperature and precipitation; the associated environmental hazard — such as increase in ground level ozone and increase in pollen; and the health impact — such as increase in skin cancer and increase in respiratory tract ailments.

The small groups discussed how climate change will impact their assigned disease and wrote the name of the disease on one card, the impact of climate change on the disease on another, and the hazard developed on a third. They then placed the cards on the board at the front of the classroom and connected them by strings to show how the different diseases share impacts and hazards.

The lesson is one of ten that EHP is developing based on the research white paper “A Human Health Perspective on Climate Change” published by EHP and NIEHS in 2010 ([see story](#)).

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Three sections of teacher Nina Daye’s advanced placement environmental science class participated in the EHP climate change lesson. (Photo courtesy of Steve McCaw)



Sen worked the room during the small group discussions, listening to the students’ responses to the reading material. (Photo courtesy of Steve McCaw)



Students connected diseases, climate change impacts, and health hazards with colored yarn to bring home the message about the complexity of climate change impact on human health. (Photo courtesy of Steve McCaw)



Carroll responded to questions and comments from students as she concluded the lesson. She told the students that she was a student in advanced placement environmental science ten years earlier during high school in Charlotte, N.C. (Photo courtesy of Steve McCaw)

Critical thinking about climate change

Toward the end of the presentation, Carroll reminded the students that their generation will be the one to witness the effects of climate change, and she encouraged them to become scientists and work toward mitigation of and adaptation to climate change.

One student remained skeptical after the lesson. “There needs to be a point where people start looking at the facts and stop just listening to what other people are saying,” he responded, but when Carroll asked if he thought he was getting the facts in class, responded, “Pretty much.”

He went on to say he believed climate change was real, but wasn’t sure how the government should deal with it. Other students were convinced that immediate steps are necessary to deal with climate change.

“Some people are skeptical, but you can see that temperatures are rising,” one said. Another referred to some data from the presentation, saying, “It’s pretty crazy that the last ice age was just 7 degrees cooler than now, and that the average temperature could go up another 7 degrees” as a consequence of global climate change.

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NIEHS takes its message on the road

By Matt Goad

The conference season gets under way Feb. 17-21 with the American Association for the Advancement of Science (AAAS) 2011 Annual Meeting in Washington, D.C. Gwen Collman, Ph.D., director of the Division of Extramural Research and Training, will give a presentation on new expectations for individuals’ right to know

in environmental health research. Banalata (Bono) Sen, Ph.D., the science education and outreach program manager for the NIEHS journal Environmental Health Perspectives (EHP) will speak about EHP's education outreach efforts.

NIEHS and National Toxicology Program (NTP) scientists will take part in the Society of Toxicology (SOT) 50th Annual Meeting March 6-10, also in Washington, D.C. ([see story](#)). NIEHS/NTP Director Linda Birnbaum, Ph.D., will speak about the future of NIEHS and NTP and emerging trends in toxicology, and NIEHS and NTP scientists will be featured in dozens of workshops.



Other major conferences NIEHS representatives will be attending this year include the Endocrine Society (ENDO) Meeting June 4-7 in Boston, the American Academy of Pediatrics (AAP) National Conference and Exhibition Oct. 15-18 in Boston, and the American Public Health Association (APHA) Annual Meeting and Exposition Oct. 29-Nov. 2 in Washington, D.C.

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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NAS series continues with workshop on microbiome

By Eddy Ball

An innovative interagency program opens its 2011 workshop series with an exploration of "Interplay of the Microbiome, Environmental Stressors, and Human Health," April 27-28 in Washington, D.C. Registration is open Feb. 1 through April 26 at the National Academy of Science's Emerging Science for Environmental Health Decisions series [Web site](#), where a tentative agenda and list of scheduled speakers will also be available.

Sponsored by NIEHS, the program holds three workshops per year on the use of new discoveries, tools, and approaches for guiding environmental health decisions. The workshops provide a public venue for communication among government, industry, environmental groups, and the academic community.

The April workshop is the sixth in the [series](#), which began in July 2009 with a workshop on "Use of Emerging Science and Technologies to Explore Epigenetic Mechanisms Underlying the Developmental Basis for Disease."

As well as providing financial support for the workshops, NIEHS grantees and leadership participate in the [steering committee](#) and [government liaisons group](#), including:

- Senior Advisor for Public Health John Balbus, M.D., chair of government liaisons
- Director Linda Birnbaum, Ph.D., member of government liaisons



NIEHS Director Linda Birnbaum (Photo courtesy of Steve McCaw)

- Grantee Kim Boekelheide, Ph.D., of Brown University, member of steering committee
- Grantee Shuk-mei Ho, Ph.D., of the University of Cincinnati, member of steering committee
- Grantee Stephen Rappaport, Ph.D., of the University of California, Berkeley, member of steering committee
- Grantee Ivan Rusyn, M.D., Ph.D., of the University of North Carolina at Chapel Hill, member of steering committee
- Grantee Helmut Zarbl, Ph.D., of the Robert Wood Johnson Medical School, member of steering committee

The group's Web site offers a wealth of information about past workshops, including videos of presentations, related resources, and the opportunity to [subscribe](#) for updates on the series, which will continue into 2013.

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Bethesda-based NIEHS Senior Advisor for Public Health John Balbus (Photo courtesy of Steve McCaw)

Search opens for NIEHS associate director for management

By Eddy Ball

NIEHS is now accepting applications for the position of [associate director for management](#). Applications will be accepted through Feb. 14.

The associate director for management is a Senior Executive Services (SES) position in the Office of the Director and serves as the principal management advisor to the director of NIEHS and senior staff. The incumbent oversees the NIEHS Office of Management, which carries out essential administrative functions, including facilities management, security, human capital management, financial management, acquisition management, management policy, supply and property management, and administrative services.

Applicants must submit a complete application and related materials electronically by the closing date of the announcement to seniorre@od.nih.gov.

Contact information:

Name: Mariela Light
Phone: 301-496-9788
TDD: 301-594-8942
Email: seniorre@od.nih.gov

Department of Health and Human Services/National Institutes of Health
31 Center Drive, MSC 2272
Bldg 31; Room 4B39
Bethesda, MD 20892-2272

Applications are also being accepted for the position of [director of the NIEHS Division of Intramural Research \(scientific director\)](#) through Feb. 28. Contact Ms. Stephanie Jones (DIR-11-01), Office of Human Resources, NIH, PO Box 12233 (MD K1-01), Research Triangle Park, NC 27709; or email collinsonj@od.nih.gov.

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Science Notebook

NTP workshop investigates links between chemicals and obesity

By Thaddeus Schug

While dietary excess and lack of exercise are well established factors fueling the obesity epidemic in the United States, new research is emerging that suggests that environmental exposures may also play a significant role in the risks associated with developing diabetes and obesity.

These linkages were the focus of an intensive three-day workshop — “Role of Environmental Chemicals in the Development of Diabetes and Obesity” — sponsored by the National Toxicology Program (NTP) Jan. 11-13 at the Marriott at Crabtree Valley in Raleigh.

The workshop brought together more than 135 scientists, representing fields ranging from molecular biology to epidemiology, to examine the science associating exposure to certain chemicals with the development of diabetes and obesity in humans. Participants also provided input on potential testing strategies, data gaps, and future research needs to address these associations. Breakout sessions were arranged to cover six particular chemical classes — arsenic and other metals, bisphenol A, organotins and phthalates, nicotine, pesticides, and persistent organic pollutants.

Smoking linked to childhood obesity

There is “good, qualitative evidence” to link maternal smoking and arsenic and persistent organic pollutants (POPS) exposure to such health conditions, according to workshop chair [Michael Gallo, Ph.D.](#), director of the Toxicology Division and the NIEHS Center of Excellence at the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey. “Some of these associations are pretty strong,” Gallo added.

“Perhaps less recognized is the consistent association of maternal smoking with increased risk of offspring being overweight or obese later in life,” said workshop organizer Kristina Thayer, Ph.D., director of the [NTP Center for the Evaluation of Risks to Human Reproduction \(CERHR\)](#).



(L-R) Shown, left to right, Gallo, Thayer, and Bucher, are all smiles following three days of intense debate. (Photo courtesy of Steve McCaw)



Expert scientists Franck Mauvais-Jarvis, M.D., Ph.D., right, and Angel Nadal Navajas, Ph.D., left, were part of a breakout group responsible for assessing the role of BPA exposure in the development of obesity and diabetes. Seated behind them is NIEHS Program Administrator Elizabeth Maull, Ph.D. (Photo courtesy of Steve McCaw)



After working in their breakout groups, participants reconvened Jan. 13 for summaries and a look at next steps. (Photo courtesy of Steve McCaw)

According to Thayer, this pattern is initially detectable in young children and continues through adulthood. It is supported by laboratory findings that monitor animals that are treated with nicotine during development.

Data plausible, but more research needed

“Like many complex diseases, it is likely that many factors contribute to the development of diabetes,” explained Thayer. “It is unknown to what extent environmental chemicals may be contributing to the current epidemics of diabetes and obesity, but it is clear that additional research is warranted to follow-up on the reported associations.”

Gallo agreed, adding, “We don’t have good animal models, and we need to deal with the human population. These data really show us that there is biological plausibility to some or all of these chemical groups.”

In concluding remarks, Jerry Heindel, acting chief of the Cellular, Organs, and Systems Pathobiology Branch of the NIEHS Division of Extramural Research and Training, said agency staff will evaluate the data needs and research strategy suggestions made by participants, and present the meeting results to its advisory group in February. The feedback will help to develop a research strategy and guide the awarding of related grants, Heindel said. “The goal is to stem the tide of the obesity and diabetes epidemic.”

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction and a regular contributor to the Environmental Factor. He is currently on detail as a program analyst in the NIEHS Division of Extramural Research and Training.)



“We may look back at this meeting in five or ten years and identify it as a watershed moment in the field of diabetes and obesity research,” said Heindel. (Photo courtesy of Steve McCaw)



Shown, left to right, expert scientist Gina Solomon, M.D., discusses outcomes of the workshop with Gallo and NIEHS/NTP Director Linda Birnbaum, Ph.D. (Photo courtesy of Steve McCaw)

A potential role for predictive toxicology

Significant discussion at the workshop centered on which types of studies, *in vitro* cell studies or whole animal *in vivo* assays, are best structured to examine the effects of environmental contaminants on metabolic disorders. Development and use of new testing methods was backed in a major National Research Council (NRC) report as a way to replace costly animal tests. However, a major hurdle pointed out by several researchers lies in how to incorporate findings from cell-based assays into reliable human risk assessment models.

According to John Bucher, associate director of the National Toxicology Program, one of the key objectives for the U.S. Environmental Protection Agency (EPA), NIEHS and the U.S. Food and Drug Administration in obesity and diabetes research is to identify new toxicity pathways and biological targets for assays that may be relevant to diabetes and obesity health outcomes and could be incorporated into EPA’s [ToxCast](#) computational toxicology database.

The ToxCast program has identified a link between a number of endpoints relevant to diabetes and obesity, such as islet cell function and insulin sensitivity, and toxicity pathways believed to be key mechanisms in metabolic disorders. “High throughput screening was not developed with this workshop in mind, but we can take advantage of ToxCast,” noted Bucher.

Miller explores the longest signaling pathway in endothelial cells

By Melissa Kerr

The brain's most effective defense against neurotoxicants is also the greatest hindrance in the delivery of potentially life-saving medicines to the central nervous system (CNS). In his Jan. 4 talk on the intricacies of the blood-brain barrier (BBB) and its seemingly paradoxical role in human health, NIEHS Senior Investigator and Acting Scientific Director [David Miller, Ph.D.](#), made a presentation about his research into “what we think is the longest signaling pathway that has been worked out in endothelial cells” and its role in BBB regulation.

Attendees at the monthly meeting of the NIEHS Receptor Mechanism Discussion Group filled the Institute's Executive Conference Room, as Miller and colleagues discussed the results of his research, the roadblocks, and the potential if researchers can discover how to successfully manipulate the BBB ([see text box](#)).

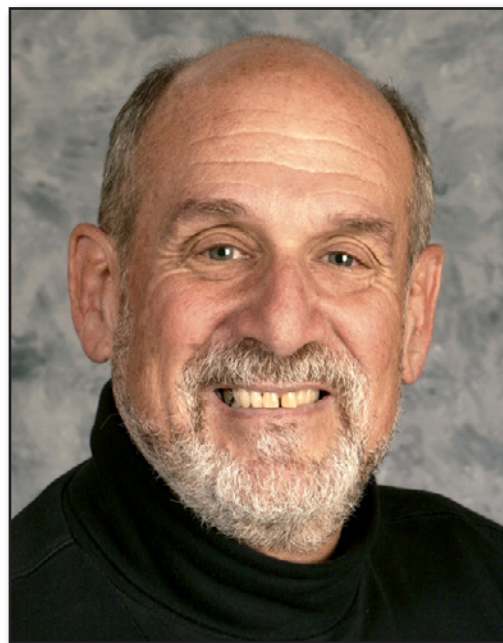
The brain protects itself

Miller described the CNS as the “final frontier” in pharmaceutical therapy because receptors along the BBB cannot distinguish between neurotoxicants and therapeutic drugs, responding to both as potentially harmful xenobiotics. The luminal plasma membrane of the brain capillary endothelium acts as a filter to regulate the exchange of material between the blood and the brain and tightens in response to expression and activity of what are known as ATP-binding cassette (ABC) transporters, especially P-glycoprotein ([see related story](#)).

Endothelial cells lining the capillaries within the brain and the transporters they express govern uptake, distribution, and excretion through the tight barriers, regulating the movement of ions, water, nutrients, and waste across the BBB. Miller and his team have been targeting how to manipulate receptors in these multiple signaling pathways to advance medicinal therapy of CNS-related diseases, better understand the mode of action of environmental neurotoxicants, and discover how harmful proteins that build up in the brain return to the blood stream for elimination.

“P-glycoprotein is the major obstacle to getting therapeutic drugs into the brain,” said Miller, “because it's at the right place to stop things from getting across the endothelium.” P-glycoprotein (Pgp) is a transporter found in high concentrations within the brain capillary endothelium.

As Miller explained, “Basically, what we're looking for is a narrow window of time to knock down p-glycoprotein activity. Then you come in with whatever drug you're trying to get into the brain, and later p-glycoprotein activity rebounds and restores protection.”



In his 2010 review, Miller pointed to the environmental and therapeutic implications of his research. “Understanding of transporter function and regulation at the human BBB is critical before we can determine to what extent signaling can be manipulated to improve drug delivery to the CNS and to enhance neuroprotection,” he wrote. (Photo courtesy of Steve McCaw)

Untying a knot within the metabolic pathway

In their early experiments, Miller's group studied mice genetically engineered to knock out Pgp expression. When these mice were treated with the opiate methadone, the researchers found seven times higher levels in the brain than in wild-type mice, confirming the importance of Pgp in BBB regulation. These results led Miller and his team to look for a way to suppress the activity of Pgp directly, but they found that drugs that specifically inhibit the transporter itself, such as PSC833, work but are moderately toxic, essentially eliminating them as viable candidates for drug development.

As an alternate plan, Miller and his group are targeting p-glycoprotein signals that maintain basal transporter activity. One signaling pathway the team found is turned on by a protein called tumor necrosis factor-alpha that reacts with receptor TNF-R1 and signals through multiple steps to cause a loss of Pgp activity. A second strategy involves manipulating expression of vascular endothelial growth factor, which also signals loss of Pgp activity.

Although the team's results have helped to elucidate extensive signaling pathways in animal models, it is not yet clear how their results will extrapolate to humans. And Miller readily concedes that there are many more twists and turns in the world's longest signaling pathway to explore in his group's quest to unravel the mysteries of the BBB.

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)

More findings from the Miller group's work on the BBB

Working from memory and without the help of a computer sidelined by technical problems, Miller developed his topic, "Receptor driven: outside in, out, in, signaling at the blood brain barrier," during a talk co-hosted by NIEHS Principal Investigators John Cidlowski, Ph.D. and Ken Korach, Ph.D. In the course of his presentation, Miller referred to several papers from his group, including the following:

- [Miller DS](#). 2010. Regulation of P-glycoprotein and other ABC drug transporters at the blood-brain barrier. *Trends Pharmacol Sci* 31(6):246-254.
- [Wang X](#), [Hawkins BT](#), [Miller DS](#). 2010. Aryl hydrocarbon receptor-mediated up-regulation of ATP-driven xenobiotic efflux transporters at the blood-brain barrier. *FASEB J*; doi:10.1096/fj.10-169227 [Online 3 November 2010]. [Story](#)
- [Hartz AM](#), [Miller DS](#), [Bauer B](#). 2010. Restoring blood-brain barrier P-glycoprotein reduces brain amyloid-beta in a mouse model of Alzheimer's disease. *Mol Pharmacol* 77(5):715-723. [Story](#)
- [Hawkins BT](#), [Sykes DB](#), [Miller DS](#). 2010. Rapid, reversible modulation of blood-brain barrier P-glycoprotein transport activity by vascular endothelial growth factor. *J Neurosci* 30(4):1417-1425. [Summary](#)
- [Hartz AM](#), [Madole EK](#), [Miller DS](#), [Bauer B](#). 2010. Estrogen receptor beta signaling through phosphatase and tensin homolog/phosphoinositide 3-kinase/Akt/glycogen synthase kinase 3 down-regulates blood-brain barrier breast cancer resistance protein. *J Pharmacol Exp Ther* 334(2):467-476. [Summary](#)
- [Bauer B](#), [Hartz AM](#), [Pekcec A](#), [Toellner K](#), [Miller DS](#), [Potschka H](#). 2008. Seizure-induced up-regulation of P-glycoprotein at the blood-brain barrier through glutamate and cyclooxygenase-2 signaling. *Mol Pharmacol* 73(5):1444-1453. [Story](#)

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Mismatch base pairing is structurally similar to correct base pairing

By Robin Arnette

When James Watson and Francis Crick published their seminal Nature papers describing the structure of the DNA double helix in 1953, they proposed that a subtle chemical change in DNA could make a mistake, or a mismatch base pair, look like a correct base pair. This hypothesis has been under investigation for more than a half century and has proven difficult to test. Now, three NIEHS investigators from the Laboratory of Structural Biology have provided strong evidence to support Watson and Crick's theory about the origin of spontaneous base substitution mutations.

Using X-ray crystallography, Katarzyna Bebenek, Ph.D., [Lars Pedersen, Ph.D.](#), and [Tom Kunkel, Ph.D.](#), have determined that human DNA polymerase can incorporate a guanine-thymine (G•T) mismatch during DNA synthesis that is structurally similar to the correct adenine-thymine (A•T) base pair. These [data](#), published in a recent 2011 issue of the journal PNAS (Proceedings of the National Academy of Sciences), are the first to show that during synthesis, natural DNA bases can form mismatches that have correct Watson-Crick geometry, potentially resulting in mutations. Interestingly, these mutations aren't due to the typical sources of environmental stress on DNA, such as exposure to UV light or chemical toxins. Instead, they happen spontaneously.

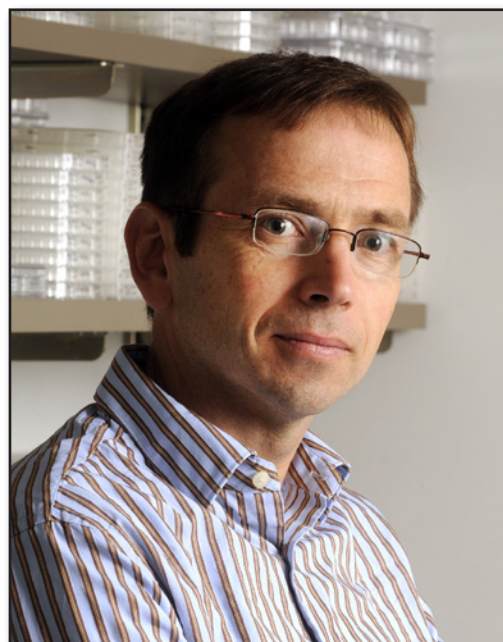
"Mutations underlying diseases do not necessarily require that a person have a genetic defect or be exposed to radiation or chemicals in the environment," Kunkel explained. "This study reveals how the chemical complexity of the genetic information can sometimes trick even a normal, healthy cell into making a mistake for good, in the case of evolution or the development of a healthy immune system, or bad, when the mutation results in disease."

Bebenek is a staff scientist in Kunkel's group and is first author on the paper. She said the results were exciting, not only because understanding how a DNA polymerase generates mutations may help scientists discern the cause of disease, but because DNA polymerases serve as targets of pharmaceutical agents. Therefore, understanding the mechanism by which DNA polymerases incorporate or misincorporate nucleotides may improve drug design.

She didn't know if scientists 50 years from now would consider this paper as important as Watson and Crick's ground-breaking publications, but she's sure that the data are solid. "While we were writing this paper, we produced another crystal structure with the same mispair, but the crystal grew under different conditions and had a different space group," she explained. "The confirmation of the mismatch, basically how it sits in the polymerase, was exactly the same. It convinced me that this mismatch didn't just happen in one crystal."



Bebenek said, "Our paper is not as groundbreaking as Watson-Crick's discovery, but it is really nice to show something that was just a hypothesis, and now we actually show that it is the case." (Photo courtesy of Steve McCaw)



Pedersen noted that he was expecting to see the guanine-thymine mismatch pair in a wobble conformation similar to what has been seen in previous crystal structures, but was elated to see the base pairs fit almost perfectly. (Photo courtesy of Steve McCaw)

As an expert on X-ray crystallography, Pedersen said that when he first saw the crystal structure, he was more excited that the active site atoms were in proper position for the catalytic reaction to proceed. It was later on that he thought about the significance of the work.

Pederson said, “Although it had been predicted to be a possibility, I was surprised to see the G•T pair with Watson–Crick-like geometry. The realization of the historical implication of this structure didn’t hit me right away.”

Although Kunkel has been involved in dozens of important discoveries related to DNA replication, he said that this work was one of the most important things his lab had ever done. He summed up his feelings by saying, “Watson and Crick’s hypothesis was a fundamental idea in molecular biology that remained unanswered for 58 years. Because we can now study DNA at the atomic level, we were able to provide strong support for an idea that had limited evidence. That’s what we’ve answered in this PNAS paper.”

Citation: [Bebenek K](#), [Pedersen LC](#), [Kunkel TA](#). 2011. Replication infidelity via a mismatch with Watson-Crick geometry. *Proc Natl Acad Sci U S A*; doi:10.1073/pnas.1012825108 [Online 13 January 2011].

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Kunkel found this work to be one of the most intellectually satisfying projects he’s participated in because it addresses an important hypothesis on the origins of mutations proposed over a half century ago by two of the founding fathers of molecular genetics. (Photo courtesy of Steve McCaw)

Faculty of 1000 highlights study by Korach group

By Eddy Ball

A paper from a team of researchers led by NIEHS Principal Investigator [Kenneth Korach, Ph.D.](#), is the first NIEHS publication to be highlighted by the Faculty of 1000 (F1000) in 2011. The study, “Uterine epithelial estrogen receptor α is dispensable for proliferation but essential for complete biological and biochemical responses,” appeared in the journal *Proceedings of the National Academy of Sciences* in November.

F1000 Editor-in-Chief Sarah Greene notified Korach of his paper’s selection Jan. 10 and congratulated him for his accomplishment, which, she said, “places your work in our library of the top 2 percent of published articles in biology and medicine.”

Korach heads the Receptor Biology Group and serves as chief of the Laboratory of Reproductive and Developmental Toxicology, which studies the mechanisms of estrogen receptor action in hormonal dysfunction and diseases, including cancers. He has edited four books and published 280 peer-reviewed articles in leading biomedical journals, as well as several book chapters.



Korach is lead investigator and corresponding author on the study. (Photo courtesy of Steve McCaw)

A work of great interest

The [study](#) was reviewed, evaluated, and rated as a “must read” by F1000 members [Jeffrey Pollard, Ph.D.](#), a researcher and Louis Goldstein Swan Chair in Women’s Cancer Research at the Albert Einstein College of Medicine, and Chellakkan Selvanesan Blesson, Ph.D., a post-doctoral fellow in the Department of Women’s and Children’s Health at the Karolinska Institutet, Stockholm, Sweden. Pollard and Blesson have several notable publications in the field of reproductive biology.

In his [comments](#) on the study, Pollard wrote, “This article is of great interest as it definitively shows that paracrine signaling is essential for uterine epithelial proliferation in the mouse. However, epithelial estrogen receptor is necessary for maintenance of viability and fertility.”

“This is fascinating as it indicates cell type-specific requirements for the estrogen receptor (ER) in uterine growth,” Pollard added. “This may mean that the regulation of cell proliferation is different in the human and mouse, and this could have profound implications for the study of human proliferative diseases.”

“This article is very exciting and provides evidence for the first time that estradiol (E2)-induced epithelial cell proliferation in the uterus is independent of epithelial estrogen receptor (ER) alpha expression,” Blesson wrote.

Evaluating top publications

[F1000](#) is a post-publication review group of thousands of experts worldwide who identify and evaluate the most important articles in biology and medical research publications. The selection process comprises a peer-nominated global faculty of the world’s leading scientists and clinicians who rate the best of the articles they read and explain their importance in approximately 1,500 reviews each month.

According to NIEHS Biomedical Librarian and Acting Library and Information Services Branch Chief Stephanie Holmgren, approximately 88 NIEHS publications have been reviewed and highlighted by F1000 since its establishment in 2002. During the past year, in addition to the paper by the Korach group, 13 NIEHS publications were rated highly by the group. Several NIEHS researchers are current or former F1000 peer-reviewers.

Citation: [Winuthayanon W](#), [Hewitt SC](#), [Orvis GD](#), [Behringer RR](#), [Korach KS](#). 2010. Uterine epithelial estrogen receptor alpha is dispensable for proliferation but essential for complete biological and biochemical responses. *Proc Natl Acad Sci U S A* 107(45):19272-19277.

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First author on the study, Wipawee Winuthayanon, Ph.D., is a research fellow in the group. (Photo courtesy of Steve McCaw)



Senior Biologist Sylvia Hewitt is second author on the paper. (Photo courtesy of Steve McCaw)

NIEHS clinical researchers highlighted in JAMA

By Eddy Ball

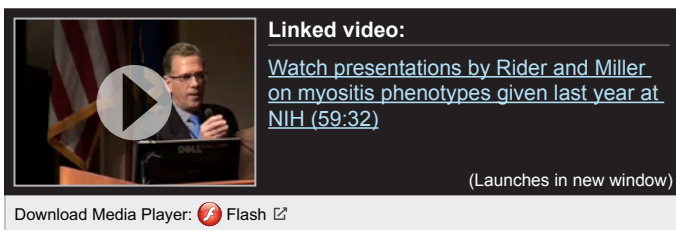
NIEHS clinical researchers are promoting a new systematic methodology for treatment of and research into a mysterious and debilitating autoimmune disease thought to be triggered by environmental exposures and genetic polymorphisms.

Their [review](#), “Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies,” appeared in the Clinician’s Corner section of the high-impact Journal of the American Medical Association (JAMA) in January.

The Bethesda-based NIEHS [Environmental Autoimmunity Group](#) Principal Investigator and Chief Frederick Miller, M.D., Ph.D., and Deputy Chief Lisa Rider, M.D., present a compelling argument for systematically categorizing heterogeneous myositis syndromes into mutually exclusive and stable phenotypes by using clinical and immune response features of the myositis syndromes.



Rider, above, delivered the first half of the NIH presentation that parallels her discussion of the various types of myositis and attendant manifestations throughout the body in the JAMA article. (Photo courtesy of Cure JM [Juvenile Myositis] Foundation)



“Research suggests that categorizing heterogeneous myositis syndromes into mutually exclusive and stable phenotypes... is useful for predicting clinical signs and symptoms, associated genetic and environmental risk factors, and responses to therapy and prognosis,” the authors conclude. “Knowledge of myositis phenotypes should enhance clinicians’ ability to recognize and manage these rare disorders.”

A rare and mysterious condition

As Rider and Miller explain, “Myositis syndromes are the most common causes of acquired muscle disease in adults, but are still rare disorders.... Epidemiological studies of U.S. populations [however] suggest these disorders are increasing in frequency, perhaps due to environmental influences.” Patients with advanced cases of myositis can be so impaired that they are confined to bed or wheelchairs. Some forms can elevate cancer risk two to four times.

Although there is evidence that a handful of genetic polymorphisms and several environmental triggers, such as infectious agents, certain drugs, ultraviolet radiation, and other exposures, are involved in myositis, the causes of these rare conditions remain unknown. According to the authors, the estimated overall prevalence of the condition is 50 to 100 cases per million, and myositis, with its unexplained skin rashes, is often misdiagnosed and undertreated in its early stages, as exemplified by the case presentation which begins the review.

According to the researchers, the need for raising physician awareness of myositis syndromes is pressing, due to the need to exclude a number of mimicking conditions in making the diagnosis. The skin rash common in dermatomyositis, for instance, can easily be confused with other skin conditions, including psoriasis and eczema, and other autoimmune diseases. Patients with polymyositis and inclusion body myositis may present with symptoms almost indistinguishable from a range of muscular dystrophies.

The next step for physicians

Practitioners, who are members of the American Medical Association (AMA) or subscribers to the AMA family of journals, can obtain [AMA Physician's Recognition Award](#) Category 1 Credit™ by reading the article by Rider and Miller and completing a brief online quiz with 60 percent or greater accuracy. These credits can count toward the annual Continuing Medical Education requirements for maintaining a valid license to practice medicine. Annual requirements vary from state to state, ranging from as few as 12 in Alabama to as many as 50 in such states as California, Pennsylvania, and Illinois.

Citation: [Rider LG, Miller FW](#). 2011. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA 305 (2):183-190.

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In his part of the NIH presentation, Miller highlighted the role of ultraviolet exposures and photosensitivity in myositis. (Photo courtesy of Steve McCaw)

Are plastics without estrogenic-active compounds possible?

By Robin Arnette

Some plastic products that previously contained bisphenol A (BPA), a chemical used to make polycarbonate plastics and epoxy resins, are now made without the chemical, due to public concern about BPA's estrogenic activity (EA) and its potential ability to interfere with the body's endocrine system and produce adverse physiological effects. Yet, according to research performed by George Bittner, Ph.D., and his colleagues at [CertiChem](#) and [PlastiPure](#), almost all commercially-available plastic products, including those sold as BPA-free, leach chemicals that exhibit detectable EA.

Bittner detailed the science behind this conclusion and its potential for helping chemists and engineers develop new and competitively priced EA-free plastics for consumers at a recent seminar held at NIEHS on Jan. 14.

[Bittner](#), a professor of neurobiology at the University of Texas at Austin and an NIEHS grantee ([see text box](#)), had CertiChem and PlastiPure staff purchase several types of plastics, such as water and soda bottles, food baggies, and deli containers, and sorted them by retailer, product type, flexibility, resin type, and whether they contained BPA. In addition, some of the pieces were microwaved, autoclaved, or subjected to UV light to simulate the stress that people place on plastic items.

Team members took a gram of each of the stressed or unstressed products, cut them into 4 millimeter squares, and extracted the material in 1 milliliter of saline or 95-100 percent ethanol. To determine EA, they evaluated the ability of the extracts to stimulate the growth, or inhibit the ability of estradiol to stimulate the growth,



Bittner titled his talk, "Most Plastic Products Release Estrogenic Chemicals: A Potential Health Problem That Can Be Solved." He believes the issue of EA in plastics is something that could be fixed, if more people were aware of the data. (Photo courtesy of Steve McCaw)

of MCF-7 cells, a human breast cancer cell line with an endogenous estrogen receptor (ER). Positive responses were verified as being ER-specific. Bittner obtained some astonishing results.

“No matter what type of extract is tested, the majority of the plastic products have EA,” he noted. “In fact, many BPA-free products release chemicals that have a greater total EA than BPA-containing products.”

Chief of the Biomolecular Screening Branch (BSB) [Raymond Tice, Ph.D.](#), served as host of the seminar and echoed Bittner’s conclusions. “Clearly, BPA is not the only estrogenic compound in plastics commonly used in the food industry,” Tice noted. “So, the goal of the plastics industry should be to formulate containers that are free of such activity rather than free of BPA only.”



Tice has held a series of seminars on new medium- and high-throughput screening methods. (Photo courtesy of Steve McCaw)

Science can lead to entrepreneurial opportunities

According to Bittner, during the production of standard plastics, manufacturers start out with a monomer, or a set of monomers, and then add other chemical agents. “After stress, many of these individual additives can leach out and display EA, so the key to making EA-free products is to find chemicals that don’t exhibit EA even after stress,” Bittner maintained. “The additional cost of making EA-free plastics is not high, typically 1 to 10 percent, when EA-containing or EA-free products are made in equal amounts. Most of that cost is attributable to testing the products to ensure they remain EA free.”

With the addition of polymer chemists to the group, Bittner’s research team was able to find several EA-free formulations for both soft and hard plastics. The work led to the creation of two companies — PlastiPure, which produces plastic containers using these plastics, and CertiChem, which tests for EA.

[Alex Merrick, Ph.D.](#), a BSB molecular toxicologist, thinks that the MCF-7 assay used in the testing “could potentially be used to monitor the safety of existing plastic products or possibly guide us in the search for newer, safer plastic products.”

Bittner’s results are promising, but more work needs to be done, such as having outside testing performed on his EA-free products. Nevertheless, the development of EA-free plastics is an important step.



Report on Carcinogens Health Scientist [Diane Spencer](#) and Host Susceptibility Branch Research Geneticist [Frank Johnson, Ph.D.](#), conferred during the question and answer session of the seminar. (Photo courtesy of Steve McCaw)

NIEHS Grants

Title: Estrogen free Polymer Formulations for Food Packaging and Baby Products

Principal Investigator: Stuart Yaniger

Institute Receiving Award: PlastiPure, Inc.

NIEHS Program Administrator: Daniel Shaughnessy

Title: A Hard and Clear, Estrogen-Free Replacement for Bisphenol-A Based Polycarbonates

Principal Investigator: Daniel Klein

Institute Receiving Award: PlastiPure, Inc.

NIEHS Program Administrator: Daniel Shaughnessy

"Phosphorylopathies," a new class of human disorders

By Negin Martin

On Jan.4, as part of the Duke University Medical Center's 2010-2011 seminar series on Ion Channel Research, NIEHS Principal Investigator [David Armstrong Ph.D.](#), gave a lecture titled "Phosphorylopathies: losing control of ion channel phosphorylation." Armstrong, who is chief of the Laboratory of Neurobiology at NIEHS, presented three examples of aberrant phosphorylation of ion channel proteins that are associated with increased risk of disease.

Inherited mutations in ion channel proteins that disrupt channel formation or ion permeation — the "channelopathies" such as epilepsy and cystic fibrosis — are one of the fastest growing categories of human disease. Channel proteins are not only responsible for the electrical signals in the brain that underlie cognition, but in most tissues, channels are the final molecular switches for maintaining physiological homeostasis. Consequently, their activity must be narrowly regulated, and ion channels have become one of the leading drug targets for pharmacological treatment of human disease.

Armstrong's group employs the patch clamp technique to study ion channels at the molecular level. By recording the picoampere currents through a single channel in the surface membrane of a cell, they can detect every opening and closing of the channel in real time *in situ*. Recent findings by Armstrong's group highlight the role of protein phosphorylation in regulating ion channels.



Armstrong, an authority on ion channel regulation, was recruited to NIEHS by former Scientific Director Martin Rodbell, Ph.D., in 1988 to establish the Membrane Signaling Group. His research is dedicated to investigating the post-translational regulation of ion channels and the signal transduction pathways that regulate them. (Photo courtesy of Steve McCaw)

Dysregulation of phosphorylation

Reversible protein phosphorylation by kinases, which add or remove phosphate groups on proteins, is a well-known mechanism for regulating protein function. However, Armstrong and his collaborators have discovered several examples in which dysregulation of phosphorylation, which they have named "phosphorylopathies," leads to loss of control of channel activity and increased susceptibility to disease. Protein phosphatases are also the target of some of the most potent microbial toxins in algal blooms, which also produce dysregulation of channel activity. During his presentation, Armstrong offered examples from his recent research that are related to human health ([see text box](#)).

Armstrong said he is pleased with the growing public interest in his field of research. "I enjoyed my visit to the Ion Channel Research Unit in the School of Medicine at Duke University," he noted. "Duke's major investment in this unit reflects the importance of ion channels in maintaining human health." He also noted that a bioinformatics group in China has now assembled a [complete list](#) of potential phosphorylopathies in the human genome, which is publicly available.

(Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology Viral Vector Core Facility and a 2009 Science Communication Fellow with Environmental Health Sciences.)

Phosphorylation dysfunction and human health

Immunosuppressants, which prevent lymphocyte activation by inhibiting the calcium-dependent protein phosphatase, calcineurin, are neurotoxic when taken chronically. In collaboration with the NIEHS Transmembrane Signaling Group headed by Lutz Birnbaumer, Ph.D., Armstrong and his group discovered that the voltage-activated CaV1.2 calcium channels encoded by the CaCNA1C gene, which link depolarization to hormone secretion, muscle contraction, and neuronal gene expression, remain open much longer when calcineurin is blocked. The resulting increase in calcium entry is toxic to neurons.

When Armstrong's group identified the amino acid in the CaV1.2 protein that is dephosphorylated by calcineurin, they discovered that a genetic polymorphism which results in Timothy syndrome, a devastating developmental disorder of brain and heart that was previously unrelated to immune suppression in transplant patients, produces a similar consensus site for the kinase at a topologically related region of the channel protein, thus exacerbating the effect of phosphorylation on channel open duration. Armstrong and his colleagues hope to use their new structural insights into calcium channel function to design drugs, such as the dihydropyridines, which are used to treat heart disease but have neurotoxic side effects that selectively block the long openings.

Building on their discovery that the polymorphism responsible for Timothy syndrome dysregulated channel activity by creating a new phosphorylation site on the channel protein, Armstrong and his group asked a summer intern to conduct a bioinformatics search for other examples in the HapMap database in which a single nucleotide polymorphism, or SNP, results in the creation or removal of a phosphorylation site in the protein. They identified fourteen additional examples where a polymorphism that was already known to be associated with human disease was also predicted to alter channel phosphorylation.

The researchers recently confirmed one of these predictions by showing that regulation of the Kv11.1 potassium channels which are encoded by the hERG gene and regulate action potential duration and frequency in cardiac myocytes, endocrine cells and neurons, reverses the effect of hormonal signaling through phosphatidylinositol 3-kinase (PI3K), a lipid kinase.

Armstrong's group had discovered previously that thyroid hormone receptors signal through PI3K to regulate Kv11 channels in pituitary cells, and they do this by stimulating a different protein phosphatase, PP5. However, PI3K is a central cellular regulator of metabolism and growth, and one of the polymorphisms in the hERG gene created a new site for a PI3K stimulated protein kinase. Consequently instead of hormonal signaling dephosphorylating and stimulating the channels and relaxing the heart, hormonal signaling now increased phosphorylation of the channels and turned them off, which is known to cause cardiac arrhythmias.

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Environmental toxicants transfer from mother to baby

By Emily Zhou

A new NIEHS-funded study has quantified for the first time the large number of environmental chemicals transferred to baby from the mother's cumulative exposure. An international team of scientists led by [grantee](#) Philippe Grandjean, M.D., Ph.D., an adjunct professor of Environmental Health at the Harvard University School of Public Health, measured concentrations of 87 environmental chemicals in both maternal and fetal tissues.

The findings of the [study](#) support the premise that pregnant and lactating mothers transfer environmental contaminants to their children, with possible risks of impairing neurological, reproductive, immunological, respiratory, and metabolic development. The team calculated partition ratios in regard to maternal serum concentrations for concentrations in maternal milk and fetal tissues. In general, a high degree of correlation was found between concentrations in maternal serum and other tissues, although the ratios differed between types of samples.

[Grandjean](#) and his colleagues were able to identify complex patterns that may help researchers pinpoint the most representative, easily obtainable samples for analyzing concentrations of specific trace elements and other compounds. As the authors cautioned in their conclusion, “These patterns are complex, and the complexity must be taken into account when selecting samples for analysis and when interpreting results.”

In a Jan. 5 [article](#) about the study in Chemical and Engineering News, [Linda Birnbaum, Ph.D.](#), NIEHS/NTP director, stressed that further studies are needed because these compounds, especially some low molecular weight polychlorinated biphenyls (PCBs), can easily cross the human placenta barrier to cord blood and milk. [Lynn Goldman, M.D.](#), dean of the George Washington University School of Public Health and Health Services, recommended policymakers consider the study’s findings when limiting women’s exposure to compounds that can potentially harm their offspring.

Telling results in a highly exposed population

To obtain systematic data about the correlation between sample types from the mother and baby, the researchers examined 15 complete sample sets of maternal and cord blood, cord tissue, placenta, and milk in connection with normal births in a fishing community of the Faroe Islands, located between Norway and Iceland. They selected this area, in part, because of the anticipated elevated exposure to marine contaminants among residents whose traditional diet includes pilot whale meat and blubber, which contain high levels of persistent pollutants such as methylmercury and polychlorinated biphenyls (PCBs).

Among their results, the researchers report that the concentration of organohalogen compounds used in solvents, refrigerants, and pesticides in a mother’s blood is highly correlated to levels in her developing baby. The team also examined correlations for the trace elements mercury, cadmium, lead, and selenium, as well several common congeners, or forms, of perfluorinated compounds (PFCs), PCBs, polybrominated diphenyl ethers (PBDEs), and other compounds.

PFCs, which are highly resistant to breakdown and are turning up in unexpected places around the world, are widely used in stain-resistant and grease-repellent products. PBDEs are persistent and bioaccumulative industrial chemicals used as fire retardants in a wide array of products. Results from this study and ongoing



According to Grandjean, almost all of the 87 chemicals were detected in both maternal and fetal tissues. (Photo courtesy of Philippe Grandjean)



The late Larry Needham headed environmental exposure measurements at the CDC and was an international leader in exposure assessment methods. (Photo courtesy of Philippe Grandjean)

investigations will help regulators identify what compounds are potentially hazardous to unborn and nursing babies, as well as determine whether reduction in organohalogen compound exposure limits are warranted.

Results from this study and ongoing investigations will help regulators to identify what compounds are potentially hazardous to unborn and nursing babies, as well as to determine whether downward revisions of organohalogen compounds exposure limits are warranted.

Scientists from Germany, Denmark, and the Faroe Islands participated in the study with Grandjean and researchers from the U.S. Centers for Disease Control and Prevention (CDC), who included the veteran CDC chemist and first author on the study, [Larry Needham, Ph.D.](#), who died before the findings were published online. In the corresponding author section of the study, the authors acknowledge his passing and write, “He will be missed both as a colleague and a friend.”

Citation: [Needham LL, Grandjean P, Heinzow B, Jørgensen PJ, Nielsen F, Patterson DG, Sjödin A, Turner WE, Weihe P.](#) 2010. Partition of Environmental Chemicals between Maternal and Fetal Blood and Tissues. *Environ Sci Technol*; Doi:10.1021/es1019614 [online 17 December 2010].

(Emily Zhou, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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Assigning a function to histone modifying enzymes

By Sophie Bolick

Sharon Dent, Ph.D., a leading scientist in the field of chromatin biology, may have had a sense of déjà vu on her recent visit to give a presentation on “The Secret Lives of Histone Modifying Enzymes” at NIEHS Jan. 13. Rising through the faculty ranks to her current position as chair of the Department of Carcinogenesis at the University of Texas M. D. Anderson Cancer Center in Smithville, Texas, Dent says she now fondly remembers her days as a postdoctoral fellow at NIH.

The [Dent](#) lab’s research program focuses on understanding the function and regulation of histone modifying enzymes and their role in cancer and other diseases, an area which has seen explosive growth since the first histone acetyltransferases were discovered in 1996. She began by describing what she thinks are the three major breakthroughs in the field over the last ten years.

The first important advance was defining the enzymes governing acetylation, methylation, and phosphorylation events at histones. Second was the finding that these modifications can regulate one another. And, third is discovering histone modifications not only alter the interactions they have with DNA, but also act as ligands for binding of other proteins.

“All of these things together have led to the idea that there’s information in these marks,” stated Dent.



Dent’s lab uses yeast and mouse models to understand the function of histone modifying enzymes. (Photo courtesy of Sharon Dent)

Cross-talk on non-histone proteins

Accurate chromosome segregation during mitosis relies on centromeres of sister chromatids to attach to microtubules from opposite spindle poles, a process mediated by kinetochores. Regulation occurs, in part, through a series of phosphorylation and dephosphorylation events. In yeast, the Aurora kinase, Ipl1, plays a key role in mediating chromosome segregation events, while Dam1 connects microtubules to the kinetochore.

One well established function for the Set1 methyltransferase is to methylate the lysine 4 residue of histone H3. Dent's group identified a novel function for Set1, separate from histone methylation, by performing a series of elegant experiments. Set1 methylates Lys233 in Dam1, which subsequently prevents phosphorylation of neighboring serines around this lysine residue from phosphorylation by Ipl1. The phosphatase Glc7 also plays an important role in maintaining just the right amount of phosphorylation for proper chromosome segregation to occur. Dent terms this the "Goldilocks model," because too little or too much phosphorylation also negatively impacts proper chromosome segregation. This finding was one of the first reports demonstrating cross-regulation on non-histone proteins.



Lecture host Trevor Archer is also principal investigator and head of the NIEHS Chromatin and Gene Expression Group. (Photo courtesy of Steve McCaw)

Gcn5 and developmental processes in mice

Dent's group also uses mouse models to study the function of histone modifying enzymes. Her work on the histone acetyltransferase Gcn5 demonstrated its involvement in mammalian development. Mice lacking Gcn5 (*Gcn5*^{-/-}) die early in embryogenesis, while mice with point mutations in the catalytic domain of Gcn5 (*Gcn5*^{hat/hat}) die later in embryogenesis and have neural tube defects. These phenotypic observations led Dent to conclude, "Gcn5 functions early in development, but independent of its histone acetyltransferase activity."

In examining the chromosomes from the *Gcn5*^{-/-} mice, it appeared they were fused together. "These turned out to be telomeric fusions that were occurring," Dent explained. Upon further analysis, there were decreased levels of the telomere-associated proteins TRF1 and POT1a in the *Gcn5*^{-/-} cells.

The SAGA complex contains numerous modules, including Gcn5 and ubiquitin-specific protease (USP22). A series of experiments showed that USP22 interacted with TRF1. Loss of Gcn5 from cells leads to a loss of USP22 from the SAGA complex, increasing TRF1 protein turnover, and thereby explaining the initial results. This was the first experimental evidence linking the SAGA complex to its role in telomere maintenance. Elucidating the function of Gcn5 is important for understanding the molecular basis of neural tube defects and cancer.

Hosted by a former postdoctoral colleague at NIH, Chief of the Laboratory of Molecular Carcinogenesis (LMC) [Trevor Archer, Ph.D.](#), Dent presented her groundbreaking research as part of the weekly LMC seminar series.

(Sophie Bolick, Ph.D., is a postdoctoral fellow with the Molecular and Genetic Epidemiology Group in the Laboratory of Molecular Carcinogenesis.)

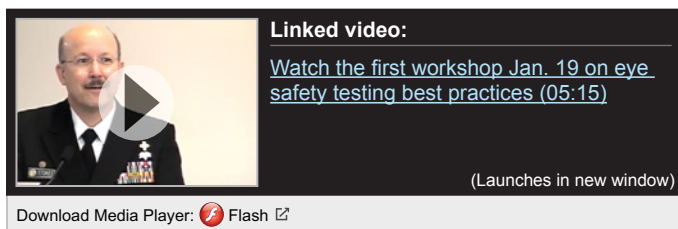
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NTP Alternatives Center Holds Workshops on Best Safety Testing

By Debbie McCarley and Cathy Sprankle

Thanks to the recent endorsement of several alternative testing methods, federal public health agencies and regulated industry now have important new tools for assessing the safety of chemicals and products.

The new test methods were the topic of two workshops on Best Practices for Regulatory Safety Testing Jan. 19-20 in Bethesda, Md., organized by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). NICEATM and ICCVAM recommended the test methods to agencies after comprehensive review of their scientific validity.



Stokes, above, also serves as the executive director of ICCVAM. (Photo courtesy of NICEATM)

The workshops addressed current best practices for safety testing necessary to determine whether chemicals and products may cause eye injuries and allergic contact dermatitis (ACD). Both types of injuries continue to have a significant impact on public health. For example, household cleaners and other chemical products are the leading cause of consumer-product-related eye injuries in children under 10. Skin diseases, including allergic skin reactions, comprise the most common category of occupational disease, and ACD accounts for an estimated 7 million health care visits each year in the United States.

Since their establishment in 1997, NICEATM and ICCVAM have contributed to the adoption of 40 alternative safety testing methods.

Ensuring worker and consumer safety

In his opening remarks, Rear Admiral William Stokes, D.V.M., NICEATM director, emphasized the important role of ICCVAM and NICEATM in translating new science from the bench into accepted and standardized test methods, such as those discussed at the workshops. “These methods can now be used as public health tools to help prevent diseases and injuries to consumers and workers by ensuring appropriate labeling of hazardous chemicals and products,” Stokes said. “The methods also minimize or avoid animal use and improve animal welfare where it is still necessary to use animals.”

Background on the Workshops

The [NICEATM-ICCVAM Five-Year Plan](#) issued in 2008 included the promotion of the regulatory acceptance and use of scientifically sound alternative test methods as a major objective. The Best Practices Workshops implement this objective by creating awareness and encouraging consideration and use of newly available accepted alternative safety testing methods. The two workshops are the first in a series on Best Practices for Regulatory Safety Testing, sponsored by NICEATM and ICCVAM, an interagency committee administered by NICEATM.

More than 70 scientists from industry, academia, and federal research and regulatory agencies gathered at the National Institutes of Health (NIH) campus for each workshop. Both workshops, which were also webcast, were co-sponsored by the Society of Toxicology and the Society for Risk Analysis.

An interagency research initiative

Stokes also highlighted the NIH and U.S. Food and Drug Administration (FDA) joint regulatory science research initiative launched last year by NIH Director Francis Collins, M.D., Ph.D., and Margaret Hamburg, M.D., FDA commissioner ([see press release](#)). The initiative seeks to accelerate the development of new tools and approaches to more efficiently and effectively evaluate product safety, efficacy, and quality. Four initial grants were awarded, including one to develop an *in vitro* test battery to determine the potential for chemicals and products to cause eye injuries.

Applying new methods — a case study approach

Eugene Elmore, Ph.D., a scientist from the University of California, Irvine and member of the federal advisory committee for NICEATM and ICCVAM, noted, “The workshop not only provided an important opportunity to explain how the new methods can be used for regulatory safety decisions, but also provided important information on how to properly conduct and interpret the assays. The successful conduct of *in vitro* assays requires careful adherence not only to all aspects of the protocol, but also to all aspects of good cell culture practices.”

Each workshop featured several case studies to allow participants to gain experience in selecting appropriate test methods and interpreting results from actual studies. Each workshop also included roundtable discussions with regulatory agencies and concluded with presentations on promising *in vitro* and *in chemico* methods in the validation pipeline. They were also the focus of many of the 35 poster presentations available for viewing throughout both workshops.

Responses from participants were overwhelmingly positive. One commented that the workshop was “an extremely helpful mechanism to bring industry and regulators up to speed and on the same page regarding what [test methods] are available, how they work, and to what extent regulators are willing to consider them.”

Presentations from the workshops are available on the [NICEATM-ICCVAM Web site](#). Plenary session presentations were webcast and are available for viewing as archival webcasts on the NIH [videocast](#) home page; a link to the archived webcast will also be available on the [NICEATM-ICCVAM Web site](#).



Shown, left to right, are the speakers and staff at the Jan. 20 workshop on allergic contact dermatitis: Stokes; Darrell Boverhof, Ph.D., The Dow Chemical Company; Michael Woolhiser, Ph.D., The Dow Chemical Company; ICCVM Vice Chair Joanna Matheson, Ph.D., Consumer Product Safety Commission; Abby Jacobs, Ph.D., Food and Drug Administration; ICCVAM Chair Jodie Kulpa-Eddy, Ph.D., Department of Agriculture; David Allen, Ph.D., principal investigator, ILS, Inc. supporting NICEATM; Judy Strickland, Ph.D., toxicologist, ILS, Inc., supporting NICEATM; Hitoshi Sakaguchi, Ph.D., Kao Corporation; Eleni Salicru, Ph.D., toxicologist, ILS, Inc. supporting NICEATM. (Photo courtesy of NICEATM)

(Debbie McCarley is the Special Assistant to Rear Admiral William Stokes, D.V.M., D.A.C.L.A.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods. Cathy Sprinkle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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This month in EHP

By Matt Goad

With its image of an ashtray overflowing with cigarette butts, the cover of the February issue of [Environmental Health Perspectives \(EHP\)](#) is a fitting backdrop for the journal's feature news story — “Does the Smoke Ever Really Clear? Thirdhand Smoke Raises New Concerns.” The article takes a look the mixture of toxicants that lingers on surfaces and resorbs into the air, well after the smoke itself clears, and discusses why some researchers believe this so-called thirdhand smoke may be a cause for concern. The issue's second news story, “Avoiding Health Pitfalls of Home Energy-Efficiency Retrofits,” examines some of the unhealthy exposures that can accompany popular home weatherization measures.

In this month's [podcast](#), NIEHS grantee and Heinz Award winner [Frederick vom Saal, Ph.D.](#), talks to host Ashley Ahearn about new research addressing the question of whether results seen in laboratory animals exposed to bisphenol A can be reasonably extrapolated to humans.

Among the reviews and research studies included in this issue are:

- Chemical Contamination of U.S. Butter
- PBDEs and Thyroid Hormone-Mediated Neuronal Development
- Mercury-Containing Products in New York City
- Heat Waves and U.S. Mortality Risk
- Arsenic-Induced Inflammation in Placenta

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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<http://twitter.com/ehponline>



Upcoming distinguished lecture by Maiken Nedergaard

By Eddy Ball

NIEHS will welcome neurosurgeon and neuroscientist Maiken Nedergaard, M.D., D.M.Sc., Feb. 8 as the next speaker in the 2010-2011 Distinguished Lecture Series. Nedergaard will explore emerging issues in translational neuromedicine in a presentation titled “Astrocyte — The Other Cell in Brain,” hosted by NIEHS Principal Investigator and Acting Scientific Director [David Miller, Ph.D.](#), head of the Intracellular Regulation Group.

[Nedergaard](#) is a professor at the University of Rochester School of Medicine and Dentistry in the Department of Neurosurgery at the Center for Translational Neuromedicine, where she is the co-director. She is also a professor in the Department of Neurology, as well as the Department of Neurobiology and Anatomy, and holds the Dean’s Professorship.

Among her many honors was her election in 2008 to the Royal Danish Academy of Sciences in recognition of her role as a pioneer in brain research, who has demonstrated that brain cells known as astrocytes play a role in a host of human diseases.

The Nedergaard lab’s interests include signaling in astrocytes and their role in seizure disorders and cerebral blood flow. She has investigated the role of gliosis — the proliferation of astrocytes in damaged areas of the central nervous system — and glial signaling in stroke and the treatment of spinal cord injury. Her group developed new modalities for imaging native and transplanted glial progenitors *in vivo*.

In recent work, Nedergaard has focused on the neurotransmitter adenosine, a nucleoside involved in sleep and one that is present in all living cells. She has explored adenosine’s role in deep brain stimulation to ease abnormal brain signaling in patients with Parkinson’s disease and other brain disorders. She has also studied the role of adenosine in pain relief experienced by patients undergoing acupuncture.



Nedergaard’s astrocyte research has challenged an earlier emphasis on the role of neurons in epilepsy, spinal cord disease, migraine, stroke, and Alzheimer’s disease. (Photo courtesy of Maiken Nedergaard)



Linked video:

[Nedergaard discusses the molecular effects of acupuncture in pain relief \(02:19\)](#)

(Launches in new window)

Download Media Player:  Flash 

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Extramural papers of the month

By Jerry Phelps

- [Mitochondrial dysfunction in children with autism](#)
- [DNA damage mapped out](#)
- [Less toxic and more effective carbon nanotubes for drug delivery](#)
- [Sperm may be harmed by BPA exposure](#)



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Mitochondrial dysfunction in children with autism

Children with autism are far more likely to have deficits in mitochondrial function, specifically in their ability to produce cellular energy, than are typically developing children. These findings are from a new study by NIEHS-supported researchers at the University of California, Davis. The results suggest that cumulative damage and oxidative stress in mitochondria could influence both the onset and severity of autism.

The brain is the second largest consumer of energy in the body, after the heart. The investigators propose that deficiencies in the ability to fuel brain cells might lead to some of the cognitive impairments associated with autism. Mitochondrial dysfunction has already been associated with other neurological diseases and conditions including Parkinson's and Alzheimer's disease, schizophrenia, and bipolar disorder.

Although the study was small, including only 10 children with autism and 10 age-matched controls, the findings may eventually help physicians provide early diagnosis. Larger studies are necessary to confirm these findings. The study does not identify the cause of autism, which affects as many as one in every 110 children, but it does offer new insights into prevention and intervention efforts.

Citation: Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN. 2010. Mitochondrial dysfunction in autism. JAMA 304(21):2389-2396. [Story](#)

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DNA damage mapped out

Using a new technique called differential epistasis maps, an international team lead by NIEHS grantee Trey Ideker, Ph.D., has documented, for the first time, how a cellular genetic network is completely reorganized in response to DNA damaging agents.

Epistasis refers to the interaction of genes and how they suppress, activate, or alter other gene's functions. To create an epistasis map, the research team focused on 400 genes that govern signal transduction pathways in yeast. They then created approximately 80,000 mutant cell lines in which each mutant line carries mutations in a different pair of the 400 genes. When the cells grow much more slowly or quickly than expected, these mutant genes are said to interact.

The map was created by identifying interactions before and after exposure to a DNA-damaging agent similar to compounds used in chemotherapy. To their surprise, the team found that most of the interactions identified after

exposure to the drug were not present without the exposure, leading them to believe that the genetic network was completely reprogrammed by DNA damage.

This discovery suggests that similar systems in more advanced organisms will be even more complex and more complicated to study. It represents a new frontier in probing dynamic interactions that enable cells to survive and thrive in varying environmental and genetic contexts. Experiments at this higher level will give scientists deeper insights into the changing environment of a living cell.

Citation: [Bandyopadhyay S, Mehta M, Kuo D, Sung MK, Chuang R, Jaehnig EJ, Bodenmiller B, Licon K, Copeland W, Shales M, Fiedler D, Dutkowski J, Guénolé A, van Attikum H, Shokat KM, Kolodner RD, Huh WK, Aebersold R, Keogh MC, Krogan NJ, Ideker T. 2010. Rewiring of genetic networks in response to DNA damage. Science 330\(6009\):1385-1389.](#)

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Less toxic and more effective carbon nanotubes for drug delivery

NIEHS-supported researchers at the University of Connecticut have found that single-walled carbon nanotubes treated with polyethylene glycol (PEG) make more effective and less toxic drug delivery vehicles than untreated nanotubes. These results give further credence to the use of drug delivery systems utilizing single-walled carbon nanotubes.

Carbon nanotubes have been touted for their potential uses in products ranging from cosmetics and drug delivery devices to the construction of a space elevator. However, concerns over their toxicity and potential to cause inflammatory reactions have hindered their uses.

The researchers layered carbon nanotubes with PEG, which has been shown to improve their dispersion in aqueous solutions. Both PEG-treated and -untreated nanotubes were then incubated with the chemotherapeutic drug cisplatin. The nanotubes were then injected into laboratory mice, and a number of cytotoxicity assays were performed. Untreated nanotubes were found to clump together in lung tissue, while PEG-treated nanotubes showed little or no accumulation. Other assays revealed biliary or renal excretion routes of PEG-treated nanotubes. PEG-cisplatin nanotubes successfully inhibited growth of head and neck tumor grafts in the laboratory mice.

Citation: [Bhirde AA, Patel S, Sousa AA, Patel V, Molinolo AA, Ji Y, Leapman RD, Gutkind JS, Rusling JF. 2010. Distribution and clearance of PEG-single-walled carbon nanotube cancer drug delivery vehicles in mice. Nanomedicine \(Lond\) 5\(10\):1535-1546.](#)

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Sperm may be harmed by BPA exposure

In one of the first human studies of its kind, researchers have found that urinary concentrations of the controversial chemical bisphenol A (BPA) may be related to decreased sperm quality and concentration. This work was carried out by NIEHS-supported scientists at the Harvard University School of Public Health.

The study included 190 men recruited through a fertility clinic. Sperm concentration, motility, shape, and DNA damage were measured in semen samples from the participants. BPA was detected in 89 percent of the men's urine samples. Sperm concentration was about 23 percent lower in men in the top quartile of exposure, as compared with the lowest quartile. The highest exposed men also had about 10 percent more damaged sperm than the lowest exposed group.

These findings are consistent with a previous study suggesting that follicle-stimulating hormone and Inhibin B concentrations are altered in response to BPA, which mimics the pattern in men with low sperm production. The researchers are continuing this line of research with a larger cohort of men, to confirm their findings.

Citation: [Meeker JD](#), [Ehrlich S](#), [Toth TL](#), [Wright DL](#), [Calafat AM](#), [Trisini AT](#), [Ye X](#), [Hauser R](#). 2010. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. *Reprod Toxicol* 30(4):532-539.

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training.)

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Intramural papers of the month

By Erin Hopper and Ritu Rana

- [MicroRNA in glucocorticoid-induced lymphocyte apoptosis](#)
- [Ubiquitination through lysine 63 mediates adhesion and migration of MDA-MB-435 cells](#)
- [The function of BAF155 in the SWI/SNF chromatin remodeling complex](#)
- [Mutation of proline 180 markedly reduces the rate of desensitization of nAChR](#)

MicroRNA in glucocorticoid-induced lymphocyte apoptosis

A collaborative study involving NIEHS, SRA International, and the University of North Carolina concluded that the expression of small noncoding microRNAs is reduced during glucocorticoid-mediated lymphocyte apoptosis, also known as immune cell death. The results suggest a role for microRNA processors and specific microRNAs in cell life and death decisions.

MicroRNAs are important regulatory elements in a cell because they are involved in development, differentiation, and apoptosis. Glucocorticoids induce apoptosis, which influences lymphocyte development. The authors found that primary microRNA transcripts were not repressed during the lymphocyte apoptosis, but key microRNA processing enzymes — Dicer, Drosha, and DGCR8/Pasha — were reduced. The investigators silenced Dicer expression in two human leukemic cell lines and saw that the depletion of Dicer enhanced glucocorticoid-induced apoptosis in both cell lines.

The overexpression of the microRNA, which is repressed by glucocorticoids, decreased glucocorticoid-induced apoptosis in both human and mouse lymphocytes, suggesting an important role for microRNAs.

Citation: [Smith LK](#), [Shah RR](#), [Cidlowski JA](#). 2010. Glucocorticoids modulate microRNA expression and processing during lymphocyte apoptosis. *J Biol Chem* 285(47):36698-36708.

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Ubiquitination through lysine 63 mediates adhesion and migration of MDA-MB-435 cells

Scientists at NIEHS recently evaluated the role of ubiquitination in arachidonic acid-induced adhesion and migration of cells from the highly metastatic breast cancer cell line MDA-MB-435. Cellular adhesion and migration are processes that are required for cancer metastasis, and previous studies from this group have established that arachidonic acid, an essential dietary fatty acid, can stimulate cellular adhesion to collagen type IV, a component of the extracellular matrix.

Although ubiquitin is well known for its involvement in protein degradation, it can function in non-proteolytic pathways as well. Ubiquitin chains linked through lysine 48 appear to target the ubiquitinated protein for degradation, but ubiquitin chains linked through lysine 63 are not as well understood and seem to play different roles in the cell, including signal transduction.

The goal of this study was to investigate the role of ubiquitin in arachidonic acid-induced cellular adhesion and migration. To this end, the researchers constructed a series of mutants in which selected lysine residues were changed to arginine, and they examined the effects of these mutations on adhesion and migration of MDA-MB-435 cells exposed to arachidonic acid. These experiments demonstrated that ubiquitination was required for cellular adhesion on collagen type IV and that polyubiquitination through lysine 63 is critical for arachidonic acid-induced cellular adhesion and migration.

Citation: Ray DM, Rogers BA, Sunman JA, Akiyama SK, Olden K, Roberts JD. 2010. Lysine 63-linked ubiquitination is important for arachidonic acid-induced cellular adhesion and migration. *Biochem Cell Biol* 88(6):947-956.

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The function of BAF155 in the SWI/SNF chromatin remodeling complex

NIEHS scientists determined that Brg-1-associated factor 155 (BAF155) plays a key scaffolding role within the SWI/SNF chromatin remodeling complex and is an important factor in the maintenance of subunit stoichiometry. The SWI/SNF complex acts to disrupt tightly packed chromatin, which allows the transcriptional machinery to access regulatory regions. This action controls the expression of genes involved in various cellular processes. The authors believe that understanding the SWI/SNF complex may lead to the identification of pathways that lead to cancer and other illnesses.

Previous studies found that BAF155 interacts and stabilizes BAF57, and that the proteasome — cellular machinery that degrades protein — regulates BAF57. The research team created BAF155 and BAF57 expression plasmids, including BAF57 mutants that lacked the principal lysine residues required for ubiquitination, and transfected UL3 cells to immunoprecipitate the proteins. They also used a small interfering RNA targeting the E3 ubiquitin ligase TRIP12 to illustrate its role in this cellular mechanism.

The study showed that TRIP12 ubiquitinates free BAF57, which targets it for degradation by the proteasome. The role of BAF155 is to interact with and stabilize BAF57 by blocking TRIP12 from adding ubiquitin molecules. BAF57 mutants incapable of being ubiquitinated could still be stabilized by BAF155, indicating an ubiquitin-independent mechanism of BAF57 degradation that involves direct interaction with the proteasome.

Citation: [Keppler BR, Archer TK](#). 2010. Ubiquitin-dependent and ubiquitin-independent control of subunit stoichiometry in the SWI-SNF complex. *J Biol Chem* 285(46):35665-35674.

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Mutation of proline 180 markedly reduces the rate of desensitization of nAChR

NIEHS researchers recently investigated the contribution of a beta-sheet proline residue to the desensitization of rat $\alpha 7$ nicotinic acetylcholine receptor (nAChR), a protein that belongs to the cys-loop superfamily of ligand-gated ion channels. When the neurotransmitter ACh binds nAChR, it leads to a conformational change that allows ions to pass through the channel pore.

Exposure of $\alpha 7$ nAChR to high concentrations of agonist results in rapid desensitization of the receptor, and this desensitization hinders efforts to perform pharmacological assays on this protein. Although the precise structure of $\alpha 7$ nAChR is not known, a number of mutations have been shown to slow the rate of nAChR desensitization. In this study, mutation of proline 180 was found to slow the rate of desensitization, and a series of mutants was created to further investigate the role of this amino acid in the desensitization of nAChR.

Mutation of proline 180 to threonine or serine dramatically decreased the rate of desensitization. The mutants P180Y and P180F exhibited a modest decrease in the rate of desensitization, suggesting that side-chain hydroxyl groups at position 180 slow desensitization but are not its sole determinant. Molecular Dynamics simulations also indicated that an increase in hydrogen bonding at position 180 may play a role in slowing desensitization.

Citation: [McCormack TJ, Melis C, Colón J, Gay EA, Mike A, Karoly R, Lamb PW, Molteni C, Yakel JL](#). 2010. Rapid desensitization of the rat $\alpha 7$ nAChR is facilitated by the presence of a proline residue in the outer beta-sheet. *J Physiol* 588(22):4415-4429.

(Erin Hopper, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Structural Biology Mass Spectrometry Group. Ritu Rana, Ph.D., is a visiting fellow in the NIEHS Laboratory of Toxicology and Pharmacology Human Metabolism Group.)

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Inside the Institute

NIEHS remembers Martin Luther King Jr.


By Melissa Kerr

NIEHS welcomed state Rep. Henry M. (Mickey) Michaux Jr. as guest speaker for a Jan. 19 tribute to the legacy of civil rights leader Martin Luther King Jr. Michaux shared his memories of working with his longtime colleague and friend. Michaux described King's achievements as a leader and the relevance of King's vision to America today.

Co-sponsored by the NIEHS Diversity Council and the Research Triangle Park Chapter of Blacks In Government (BIG), the observance opened with remarks from host and BIG Chapter President Veronica Godfrey Robinson, who also led the audience in singing the opening verse of "We Shall Overcome."

Chris Long, NIEHS acting associate director of management, followed with a personal — and at times emotional — reflection on how major events in the civil rights struggle of the early 1960s intersected with his childhood. "You can't just read about history. You have to connect with it somehow," Long insisted. "So I am particularly interested in hearing what Representative Michaux has to say today."



Long recommended that people in the audience take the time to revisit King's famous "I Have a Dream" speech to remember how King's words inspired the nation.



Linked video:

[Take Long's advice and experience the power of King's most famous speech once again \(11:51\)](#)

(Launches in new window)

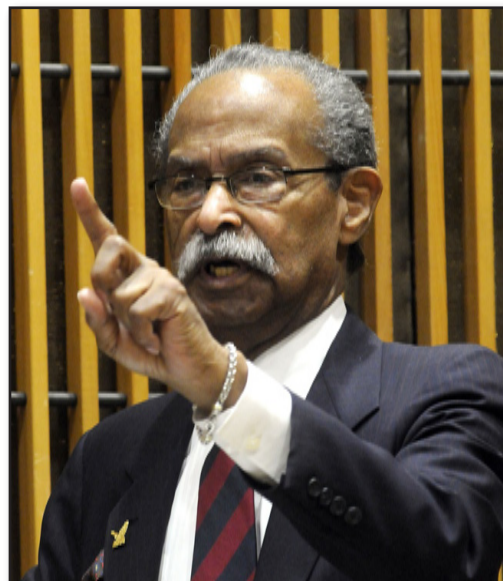
Download Media Player:  Flash 

Bringing history to life

Although Michaux humanized this American legend with his anecdotes and quips about their time together, he said he wanted to give thanks and to celebrate King's larger-than-life achievements. "[King's] struggles were inspired by his religious faith," Michaux said. "The depth of meaning of his life is unfathomable and inexhaustible."



Long mixed gravity with self-deprecating humor as he recalled his childhood in Chapel Hill, N.C., as America underwent tremendous social change during the 1960s. (Photo courtesy of Steve McCaw)



Referring to agape, the Greek word for unconditional love, Michaux shared his enthusiasm for King's message of love and respect for all mankind. He received a standing ovation for a speech filled with humor, emotion, and motivation. (Photo courtesy of Steve McCaw)

The two first met in October 1956, when Michaux invited King to speak before a Durham business group. “Martin really moved that community at that time,” he said.

Michaux recalled the hot summer day in August 1963 in Washington, D.C., when he stood with the crowd of 200,000 and listened to King deliver a speech, which, Michaux said, “rang out across the country; echoing our hopes, refocusing our ideals, and summoning our better selves.”

Michaux shared several fond memories of King, the man, who stayed with Michaux’s family during visits to Durham. “Preachers love to eat,” he joked. “I didn’t know whether or not his staying with us every time he was in North Carolina was a result of my titillating conversation or my mother’s cooking.”

Michaux recalled a time when he accompanied King to five different presentations on the same day in Raleigh and Durham. King sat in a chair before each speech and very quickly memorized what he intended to say. According to Michaux, throughout the five different speeches, King never said the same thing twice.

A timeless message

“The last time I talked with Martin was in 1968,” Michaux said. King had canceled a political tour with Michaux because he felt he had to return to Memphis where he was assassinated a few days later.

In reflecting on King’s importance to subsequent generations, Michaux insisted that the message of community love and respect is needed today. “I celebrate with pleas for aggressive political participation,” Michaux closed, “because it represents the most effective way to empower the disadvantaged, to give voice to the voiceless, to give substance to the invisible and in the process achieve true greatness for America.”

Michaux is the longest-serving African American member of the North Carolina General Assembly. With the exception of a four-year period between 1979 and 1984, he has represented the 31st House district continuously since 1972.

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)

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Shown, left to right, NIEHS employees Darlene Dixon, Ph.D., John Schelp, and Elena Braithwaite, Ph.D., laughed as Michaux delighted the audience with personal stories about King. (Photo courtesy of Steve McCaw)



Robinson, center, and NIEHS Diversity Council Chair Brad Collins, right, presented Michaux with a copy of the poster announcing his talk. (Photo courtesy of Steve McCaw)



Among several personal friends Michaux, right, talked with following the presentation was NIEHS contractor Elliott Gilmer. Gilmer, who attends the same Durham church as the speaker, said afterwards, “Mickey and I go back 57 years.” (Photo courtesy of Steve McCaw)



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